

**IN THE UNITED STATES DISTRICT COURT FOR THE
WESTERN DISTRICT OF PENNSYLVANIA**

BEST MEDICAL INTERNATIONAL, INC. Plaintiff, vs. ACCURAY, INC., a corporation; Defendant.	Case No. 2:10-CV-1043 (TFM)
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DECLARATION OF DR. ISAAC I. ROSEN

I, Isaac I. Rosen, Ph.D., submit this declaration in support of Defendant Accuray Incorporated's ("Accuray") proposed claim constructions and its brief in support of its claim construction.

I. QUALIFICATIONS

1. I am currently a Radiation Physicist at The Methodist Hospital in Houston, Texas, where I have been since January 2009.

2. I was a Radiation Physicist at The Mary Bird Perkins Cancer Center in Baton Rouge, Louisiana and an Adjunct Professor at Louisiana State University in Baton Rouge, Louisiana from February 2006 until August 2008. This was part-time consulting employment.

3. I was a Radiation Physicist and faculty member (Associate Professor, Professor) at the University of Texas M. D. Anderson Cancer Center in Houston, Texas from September 1993 until December 2005.

4. I was a Radiation Physicist and faculty member (Assistant Professor, Associate Professor) at the University of Texas Medical Branch in Galveston, Texas from March, 1983 until August 1993.

5. I was a Radiation Physicist at the University of New Mexico in Albuquerque,

New Mexico from 1975 until 1983.

6. I was a Research Assistant at the University of Texas M. D. Anderson Hospital and Research Institute in Houston, Texas from 1974 until 1975.

7. I received my B.S. degree in physics from the University of California, Los Angeles, in 1968. I received my M.S. degree in physics from California State University, Northridge in 1974. I received my Ph.D. degree in physics from the University of New Mexico, Albuquerque in 1982.

8. In addition:

(a) I am a Professor Emeritus at the University of Texas M. D. Anderson Cancer Center in Houston, Texas.

(b) I am a Fellow of the American Association of Physicists in Medicine.

(c) I am Board Certified in Therapeutic Radiological Physics by the American Board of Radiology.

(d) I am Board Certified in Radiation Oncology Physics by the American Board of Medical Physics.

(e) I am licensed by the Texas Board of Licensure for Professional Medical Physics.

9. For approximately 14 years (1986-2000), my research focused on the mathematical optimization of radiation therapy treatment plans. My research was supported by a grant of \$1,000,000 from the National Cancer Institute and grants from the Whitaker Foundation and the Houston Institute for Cancer Research, Detection, and Treatment. This research program produced 17 peer-reviewed publications and 5 book chapters. I gave over 20 invited presentations, many at national and international meetings.

10. I have also conducted research in other aspects of radiation therapy treatment planning, software development, radiation dosimetry, intensity-modulated radiation therapy (IMRT), and quality assurance in radiation therapy. These research projects resulted in an additional 72 peer-reviewed publications, 7 book chapters, and numerous presentations at national and international meetings. I have also chaired invited and proffered scientific sessions at national and international conferences

11. I have been retained by Accuray as an expert witness in this case.

12. I have been asked to opine about the technology at issue in the '283 patent.

13. If called as a witness, I expect to provide opinions and testimony on the background and state of the art related to the '283 patent.

14. My most recent Curriculum Vitae is attached as Exhibit 1.

15. My research related to the subject of this patent is attached as Exhibit 2.

II. PRIOR TESTIMONY AND COMPENSATION

16. In the last four years, I have not testified as an expert by deposition. I have not testified as an expert at trial.

17. I am being compensated for my work on this case at a rate of \$350 per hour plus expenses. My compensation is not contingent upon any outcome of this case.

III. PERSON OF ORDINARY SKILL IN THE ART

18. I understand that, when reading a claim of a patent, the terms that are presented are to be reviewed as they would be understood by one of ordinary skill in the art.

19. It is my understanding that the courts have instructed that, in determining the level of ordinary skill in the art, one should consider: (1) the educational level of the named inventor(s); (2) the type of problems encountered in the art; (3) prior solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6)

educational level of active workers in the field). *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007)

20. In my opinion, with respect to the '283 patent, a person of ordinary skill would be a medical physicist with training in mathematical optimization algorithms. Such a person would have a Ph.D. in physics, medical physics, or a related science, at least 5 years of practical experience in radiation treatment planning, and at least several years of research in treatment plan optimization.

IV. SUMMARY OF ACCURAY'S CLAIM CONSTRUCTION

21. I understand that Accuray construes the phrase "**an apparatus for determining an optimized radiation beam arrangement**" to mean "a computer configured to use the simulated annealing ("SARP") optimization algorithm to determine the optimal array of beam weights for the beam elements at each orientation based on the treatment objectives as expressed in the cost function incorporated in the SARP algorithm." Accuray construes "**an optimized radiation beam arrangement**" to mean "the optimal array of beam weights for the beam elements at each orientation based on the treatment objectives as expressed in the cost function incorporated in the SARP algorithm." I agree with Accuray's construction, and it is my opinion that one skilled in the art would interpret this phrase in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the '283 patent was filed.

22. I understand that Accuray construes the phrase "**a computer, adapted to computationally obtain a proposed radiation beam arrangement**" to mean the following:

a. Accuray construes "**a computer**" to mean "the specific computer that performs the beam weight optimization. That computer is configured with and running plan optimization software, including the simulated annealing algorithm, which performs

the beam weight optimization.”

b. Accuray construes “**adapted to computationally obtain**” to mean “configured to run the Simulated Annealing algorithm (“SARP”) to calculate ‘a proposed radiation beam arrangement. The computer is loaded with and runs plan optimization software that includes the simulated annealing algorithm to calculate “a proposed radiation beam arrangement.”

c. Accuray construes the phrase “**a proposed radiation beam arrangement**” to mean “an array of proposed beam weights for the beam elements at each orientation calculated using the simulated annealing (“SARP”) algorithm during a given iteration of the simulated annealing (“SARP”) algorithm from the partial volume data input by the user for each target and structure.”

I agree with Accuray’s construction, and it is my opinion that one skilled in the art would interpret this phrase in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the ‘283 patent was filed.

23. I understand that Accuray construes the phrase “**the computer further adapted to computationally change the proposed radiation beam arrangement iteratively**” to mean the computer is “configured to run the Simulated Annealing algorithm (“SARP”) to change ‘the proposed radiation beam arrangement’ (defined above) by adding or subtracting beam weights to beam elements randomly at each iteration (or each cycle) of the SARP algorithm.”

a. Accuray construes the phrase “**Further adapted to**” to mean “configured to run the same optimization algorithm as above, the simulated annealing algorithm (“SARP”).”

b. Accuray construes the term “**computationally change**” to mean “using the simulated annealing algorithm (“SARP”) to add or subtract beam weight to the beam elements randomly.”

c. Accuray construes the term “**iteratively**” to mean in cycles of the simulated annealing (“SARP”) algorithm.

I agree with Accuray’s construction, and it is my opinion that one skilled in the art would interpret this phrase in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the ‘283 patent was filed.

24. I understand that Accuray construes the phrase “**changing the beam weights**” to mean “adding or subtracting small quanta of positive and negative beam intensities to the beam elements randomly at each iteration of the simulated annealing (“SARP”) algorithm.” Accuray construes the phrase “**beam weights**” to mean “beam intensities.” I agree with Accuray’s construction, and it is my opinion that one skilled in the art would interpret this phrase in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the ‘283 patent was filed.

25. I understand that Accuray construes the phrase “**the computer further adapted to incorporate a cost function at each iteration**” to mean: “the computer configured to run the simulated annealing (“SARP”) algorithm incorporates a ‘cost function’ in each cycle of the SARP algorithm.”

a. Accuray construes the term “**cost function**” to mean the cost function defined at column 13, lines 4-39 of the ‘283 patent, including each of the steps described therein.

b. Accuray construes the phrase “**at each iteration**” to mean “at each cycle

of the simulated annealing ('SARP') algorithm."

I agree with Accuray's construction, and it is my opinion that one skilled in the art would interpret this term in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the '283 patent was filed.

26. I understand that Accuray construes the phrase "**to approach correspondence of partial volume data associated with the proposed radiation beam arrangement to partial volume data associated with a pre-determined desired dose prescription**" as follows:

a. Accuray construes "**to approach correspondence**" to mean "the cost function calculates a total dose cost for the change to the proposed radiation beam arrangement which is a metric for how close the partial volume data (or CDVHs) of the proposed radiation beam arrangement of the current iteration is to the partial volume data (or CDVHs) of the desired dose prescription. The partial volume data and CDVH's are for the target and each involved structure. To approach correspondence means minimizing the difference between the proposed radiation beam arrangement and the desired dose prescription."

b. Accuray construes the phrase "**partial volume data**" to mean: "numerical values corresponding to values represented as specific data points on CDVH curves associated with each target and each involved structure."

c. Accuray construes the phrase "**partial volume data associated with the proposed radiation beam arrangement**" to mean: "Numerical values corresponding to values represented as specific data points on CDVH curves associated with each target and each involved structure based on the proposed radiation beam arrangement, which

data points define the CDVH curves and the proposed zones incorporated in the cost function; generated within a given iteration of the simulated annealing (“SARP”) algorithm.”

d. Accuray construes the phrase **“partial volume data associated with predetermined desired dose prescription”** to mean: “Numerical values corresponding to values represented as specific data points on CDVH curves for each target, including at least: the minimum dose to be received by any portion of the target volume that will be underdosed [A], the desired dose to be achieved in the target volume [Bd], the portion of the target volume which should have a dose greater than the goal [Bv], and the target maximum dose value to be received by any portion of the target [C], and for each structure, including at least the desired dosage limit not to be exceeded in the volume of a sensitive structure [Bd’]; the maximum dose to be received by any portion of the structure [C’] ; the dose below which there is no appreciable benefit gained by reducing the exposure to the structure [A’]; and the portion of the structure volume which can have a dose greater than the goal dosage may be represented by structure percent over limit value [Bv’]; which data points define the CDVH curves and the zones incorporated in the cost function. Partial volume data are input into the prescription panel and are associated with the predetermined desired dose prescription.”

I agree with Accuray’s construction, and it is my opinion that one skilled in the art would interpret this phrase in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the ‘283 patent was filed.

27. I understand that Accuray construes the phrase **“the computer further adapted to reject the change of the proposed radiation beam arrangement if the change of**

the proposed radiation beam arrangement leads to a lesser correspondence to the desired dose prescription and to accept the change of the proposed radiation beam arrangement if the change of the proposed radiation beam arrangement leads to a greater correspondence to the desired dose prescription to obtain an optimized radiation beam arrangement” to mean: “the same computer uses the same simulated annealing optimization algorithm (“SARP”) to reject . . . or to accept . . .”

- a. Accuray construes the phrase **“the change of the proposed radiation beam arrangement”** to mean: “the new array of proposed beam weights for the beam elements at each orientation resulting from using the simulated annealing (“SARP”) algorithm to add or subtract beam weight randomly during a given iteration. Or in other words, it is the new proposed solution of beam weights at a given iteration of the simulated annealing algorithm after changing the beam weights.”
- b. Accuray construes the term **“correspondence”** to mean: “The cost function calculates a total dose cost for the change to the proposed radiation beam arrangement which is a metric for how close the partial volume data (or CDVH) of the proposed radiation beam arrangement of the current iteration is to the partial volume data (or CDVH) of the desired dose prescription. To approach correspondence means minimizing the difference between the proposed radiation beam arrangement and the desired dose prescription, or in other words, to minimize the total dose cost.”
- c. Accuray construes the phrase **“leads to a lesser (greater) correspondence”** to mean: “Comparing the total dosage cost (the output of the cost function) of the changed proposed radiation beam arrangement from the current iteration to the total dose cost (the output of the cost function) of the proposed radiation beam

arrangement from the previous iteration. If the total dosage cost of the changed proposed radiation beam arrangement of the current iteration is less than the total dosage cost of the proposed radiation beam arrangement from the previous iteration, the change to the proposed radiation beam arrangement is accepted. If the total dosage cost of the change to the proposed radiation beam arrangement from the current iteration is greater than the total dosage cost of the proposed radiation beam arrangement from the previous iteration, then the change to the proposed radiation beam arrangement is rejected.”

d. Accuray construes the phrase **“to obtain an optimized radiation beam arrangement”** to mean to obtain “the optimal array of beam weights for the beam elements at each orientation based on the treatment objectives as expressed in the cost function incorporated in the SARP algorithm.”

I agree with Accuray’s construction, and it is my opinion that one skilled in the art would interpret this phrase in this way, in view of the specification, the file history and the general knowledge of those skilled in the art at the time the ‘283 patent was filed.

28. I reserve the right to supplement or modify my opinions, if warranted, and to offer additional testimony rebutting any evidence or arguments advanced by Best Medical International Inc. (“Best Medical” or “BMI”) or any other witness, and to comment on any declarations and/or reports submitted in connection with this motion and litigation. I may also testify in rebuttal to testimony or opinions offered by other witnesses. At any hearings regarding this brief, I may rely on visual aids and demonstrative exhibits.

V. MATERIALS CONSIDERED

29. The bases for my opinions herein and any testimony that I may be called upon to give are the materials identified throughout my Declaration and Exhibit 3, my education, my vast experience, as well as the materials listed in my declaration and/or submitted by the Parties

in their Joint Disputed Claim Terms Chart pursuant to Local Patent Rule 4.2.

VI. BACKGROUND

A. Overview of Radiation Therapy

30. Radiation therapy (also called radiation oncology, radiotherapy, and therapeutic radiology) is the medical use of high doses of ionizing x-ray radiation, typical in the MeV (million volt) energy range. These doses are distinguished from the much lower doses of ionizing x-rays used for medical imaging, which are typically in the kV (thousand volt) range. Today, radiation therapy is most often used in cancer treatment to kill malignant cells (radiation oncology). Radiation therapy is a localized treatment, similar to surgery, and unlike systemic treatments (treatment of the whole system) such as chemotherapy. It may be curative by itself for some types of cancer if they are localized to one area of the body. It may also be used as part of multidisciplinary curative cancer therapy to eliminate residual or microscopic disease following surgery to remove a primary malignant tumor (for example, early stages of breast cancer).

31. Radiation therapy is applied to cancerous tumors because of its ability to kill cells, primarily by damaging the DNA. In order to reach the tumor, therapeutic radiation must pass through normal, healthy tissues. Because ionizing radiation will also kill normal cells, two strategies are employed to limit the damage to normal tissues. One strategy is fractionation, in which the dose needed to kill the tumor is delivered as a series of smaller doses over a period of time, typically on the order of tens of days for conventional radiation. Normal cells are able to recover from radiation damage more readily than cancer cells, so the normal cells "heal" to some extent between fractions while the damage to the cancer cells accumulates, leading to their ultimate demise over the course of treatment. The second strategy is to minimize the doses to the normal tissues. When treating with external beams of radiation, minimizing doses to normal tissues is accomplished by using multiple shaped beams from many different directions. The

dose is highest where the beams intersect at the tumor. Techniques for shaping the external beams and minimizing normal tissues doses have improved over time with advances in computer and linear accelerator technologies.

32. Medicine has used radiation therapy as a treatment for cancer for more than 100 years, starting within a few years of the discovery of x-rays by Wilhem Roentgen in 1895, the discovery of radioactivity by Henri Becquerel in 1896, and the discovery of polonium and radium by Marie Curie in 1898. The efficacy of fractionated radiotherapy for the treatment of cancer was first demonstrated by Henri Coutard in 1922.

33. Early radiation therapy treatments used radium for brachytherapy (placement of radioactive seeds or needles directly into the tumor) and orthovoltage x-ray machines for external beam therapy. Over time, radium was replaced by other isotopes for brachytherapy (primarily cesium-137, iodine-125, iridium-192, and palladium-103). Treatment machines for external beam therapy using more penetrating megavoltage energies were first developed in the 1940's with cobalt-60 sources. In the 1950's, external beam treatment machines ("linacs") were created that incorporated linear accelerators for the x-ray source rather than radioactive isotopes. Cobalt-60 machines and linacs rapidly superseded the orthovoltage machines and today, in developed countries, linacs have virtually eliminated cobalt-60 machines.

34. Early external beam treatments used film radiographs to design the shapes of the x-ray beams. These beam shapes were usually based on the positions of the bones, visible on standard x-ray images (the radiographs). The position of the actual target was inferred from the bony anatomy. The actual shaping of the beams was accomplished using individually manufactured radiation shields. The shields were manually made and placed between the patient and the x-ray source.

35. The invention of computed tomography (CT scans) in the 1970s allowed physicians for the first time to visualize the interior of the body in three dimensions with great detail and accuracy. The 3D images are obtained by rotating a lower energy (kV) imaging source around the body with a detector opposite the source to collect the data. After the source completes a rotation, the patient is moved through the scanner for another rotation of the source and detector. The data collected are reconstructed for each rotation to provide a 2D image of that “slice”, and all the slices are reconstructed to obtain the 3D image of the patient. CT-based planning for radiation treatments began almost as soon as manufacturers began producing commercial CT scanners.

36. Although CT images could provide 3-dimensional views of the patient, the computers in the 1970s lacked sufficient processing power or graphical displays to utilize the 3D information in treatment planning. The era of 3D treatment planning began in the mid-1980s with the development of virtual simulation by Sherouse and others.

37. Initially, 3D treatment planning consisted of using three-dimensional views interactively to select directions for beams and to design beam shapes. Today, the 3D CT data are also used in the calculation of the radiation doses, so that doses are known much more accurately.

38. With the advent of 3D CT-based treatment planning, there was greater information about the internal normal structures as well as the target. This new information spurred a growth of research into computer methods for optimizing radiation treatments.

39. Concurrently, the development of magnetic resonance imaging (“MRI”) in the 1970’s and positron emission tomography (“PET”) in the 1980’s gave us the ability to visualize soft tissue (MRI) and metabolic activity (PET). These imaging modalities have continued to

improve and now play an integral role in defining tumor and normal tissues during treatment planning and in following the response to treatment.

40. Although the term "3D conformal radiation therapy" (3DCRT) was coined in the 1990's, 3DCRT was a development that evolved gradually from the mid-1980's as computers and treatment planning systems became more powerful and able to more fully use the 3D images from CT. The concept of 3DCRT is to shape the internal high dose delivered to a target volume as closely as possible to the shape of the tumor target volume while limiting doses to normal structures. With a gantry-based radiotherapy system, this is accomplished by choosing optimum directions for the multiple beams and shaping each beam to the shape of the target.

41. A conventional gantry-based radiotherapy linac rotates the radiation source about the patient in a single plane. Usually, the plane is transverse to the patient's body axis, the same planes as CT images. The patient lies on a couch that moves in three directions and rotates in opposition to the gantry rotation. By rotating the couch, the radiation source can be aimed at the patient from a variety of directions other than transverse. The beams are shaped by multileaf collimators whose operation is described below in more detail.

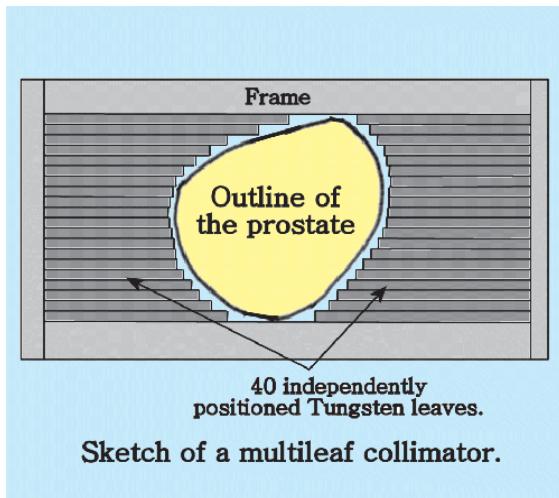
B. Multileaf Collimators (MLCs) and the Advent of IMRT

42. Manufacturers began incorporating multileaf collimators (MLCs) into their linear accelerators (linacs) in the 1990's. MLC's shape (or collimate) the radiation beam using narrow leaves of tungsten. The leaves move independently under control of a computer. There are two types of multileaf collimators - continuous and binary. In both types, the tungsten leaves are arranged in two opposing banks.

43. With a few exceptions, treatment machines are designed to deliver beams of radiation with constant intensity. "Intensity" or "fluence" is the amount of radiation passing through the cross-sectional area of the beam at any moment. When the intensity is not uniform

across the treatment beam, the pattern of intensities across the treatment beam is called the "intensity map".

44. With the continuous MLC, the leaves can move large distances across a large radiation field and stop at any position within the field. These MLC's are the most common. They are used to shape the radiation beam and eliminate the need for manually-constructed radiation shields ("blocks"). Below is a sketch of a typical MLC used in radiation therapy. The sketch is presented from a "beam's eye view" looking down at a patient. There are two banks of opposing leaves, where each leaf can move independently in and out of the beam path. For example, if all the leaves are in the fully open position, then a rectangular-shaped beam or field would be passed through the collimator. The leaves can form rather complex shapes, and as the gantry rotates to different gantry angles, the shape of the MLC can be changed to accommodate the different shape a target may have from each angle. In this manner, complex dose deliveries are possible. The leaves can also be moved during radiation exposure to produce optimized intensity maps.



45. In binary MLC's, the leaves have only two positions, corresponding to open and closed. As with the continuous MLC, the leaf positions are controlled by computer. For these

MLC's, the leaves divide the radiation beam into beamlets (or beam elements). The computer controls whether the individual leaves of the MLC are open or closed, and for how long. The amount of time that a leaf is open determines the beam intensity from the particular beamlet corresponding to that leaf. The intensity is increased by leaving the leaf open for a longer period of time. Think of the shutter of a camera. The camera shutter stays open for a certain period of time and then closes, letting light in only for that period of time. The amount of time the shutter is open changes the exposure of the film. Each tungsten leaf of a binary MLC is like the shutter of the camera. While the radiation source is pointing at the patient from a given direction, each leaf can be open for a different period of time, thereby delivering a different intensity from each beamlet. The overall result is to deliver a beam of radiation from that direction whose intensity varies from point to point. The development of MLCs was an enabling technology for intensity-modulated radiation therapy (IMRT), the next stage in the evolution of external beam radiation therapy.

46. IMRT can create complex dose patterns that are not possible with 3DCRT. For example, IMRT dose distributions can conform to target volumes with concave shapes. This is essential when a tumor wraps around a critical structure such as the spinal cord. They can also produce steep dose gradients that are very beneficial when targets are abutting important normal structures, such as the rectum in prostate treatments. As with other techniques, the goal is to maximize the dose to the target while simultaneously limiting the doses to normal tissues.

47. When IMRT is delivered using a continuous MLC, the radiation intensity is modulated at a particular gantry angle by changing the shape or collimation of the beam while the radiation is being delivered. At each moment, the MLC forms a shape that covers only part of the target. As the radiation continues, the MLC shapes changes to cover different parts of the

target for different periods of time. In this manner, the amount of radiation (intensity) hitting the target is different from point to point from that particular beam direction.

48. In IMRT, radiation intensity in each beam is varied across the silhouette of the target in such a way that the dose pattern from all the beams combined produces the optimum 3D dose pattern. Note that the radiation intensity pattern from each beam alone is not optimum. Only all beams together give the optimum dose distribution within the patient. In other words, the concept of IMRT is to deliver multiple beams with unique, non-uniform intensity maps coordinated in such a way that when all of the beams are delivered the dose distribution inside the patient is optimal. Each IMRT beam is subdivided into many small "beamlets," each of which has a different beam intensity.

49. A beam weight is the amount of radiation delivered by a beamlet relative to the amounts delivered by other beamlets. For example, if one beamlet has twice the weight of another beamlet, it will deliver twice as much radiation. Because beam weights are relative, doubling all of the weights for a beam from a particular direction, doubles the amount of radiation delivered by that beam, but does not change the pattern of intensity. It would have the same effect as leaving the radiation on for twice as long. Usually, the weights of the beamlets are normalized, which means that they are fractions of 1 such that their sum is equal to 1. Consequently, if one beamlet weight is changed, other beamlet weights must also change so that total is still equal to 1. For example, assume that we have 5 beamlets with weights of 0.1, 0.3, 0.3, 0.2, and 0.1. If the weight of the first beamlet is increased to 0.4, then the weights of one or more of the other beamlets must decrease such that the remaining beamlets have a total weight of 0.6 and all 5 beam weights still add up to 1. Beam weights determine the radiation doses in the patient, but they are not doses. In a general sense, the physician's treatment prescription is used

to convert beam weights to doses. For example, if the physician prescribes 60 Gy to the tumor, then the beamlets above would deliver doses of approximately 6 Gy, 18 Gy, 18 Gy, 12 Gy, and 6 Gy.

50. Radiation doses are measured in units of gray (Gy). Each Gy corresponds to a fixed amount of energy absorbed in tissue (1 joule/kg). Cell killing is a function of the amount of energy absorbed by the cell. Therefore, the amount of cell kill is related to the dose delivered to the cell, expressed in Gy. Today, radiation prescriptions are written in units of gray. However, the older unit of radiation dose, the rad, is still in the literature, and 1 Gy = 100 rad.

51. In IMRT planning, there may be hundreds to thousands of beamlets, all of whose weights need to be optimized. By comparison, in 3D conformal radiation treatment planning, there is usually only one weight per beam and typically no more than a dozen beam weights total to be optimized. Because of the complexity of determining so many beam weights, IMRT planning is not possible without a computer running an optimization algorithm. Optimization algorithms are discussed in more detail below.

52. The practice of radiation therapy includes many different treatment techniques and technologies (brachytherapy, x-ray beam, electron beams, etc.), and the most appropriate of these is chosen for each patient based on their disease and clinical situation. IMRT is now a well-established part of that treatment arsenal.

C. Treatment Planning

53. The process of designing the details of the treatment for a particular patient is called "treatment planning". With external beam radiation, treatment planning typically consists of (1) obtaining a diagnostic quality 3D CT image of the patient prior to treatment; (2) delineating/contouring/segmenting the shapes of the target(s) and normal structures on the relevant images, (3) deciding on the doses to be delivered to the target and the amount of dose

allowed to normal structures (prescription), (4) selecting the type of radiation and energy, (5) selecting the number of radiation beams and their gantry angles (in the case of conventional gantry-based delivery), (6) designing the shape or collimation of each beam, (7) and deciding how much radiation to give from each beam. For non-IMRT beams, deciding how much radiation to give from each beam usually means manually selecting a weight for each beam. For IMRT planning, deciding how much radiation to give from each beam means using inverse planning to design the intensity maps for the beams. Computer automation and optimization techniques are used to varying degrees in all of these steps.

54. The treatment planning team consists primarily of the radiation oncologist, the medical physicist, and the dosimetrist. Occasionally a radiologist, neurosurgeon, or other medical specialist may participate in the determination of tumor volume and normal anatomy. The radiation oncologist defines the anatomy and dose prescription. The medical physicist and dosimetrist create a treatment plan by designing the details of delivery. The resulting doses in the patient ("dose distribution") are reviewed and approved by the radiation oncologist. Most often this is an interactive process among the participants.

55. One way that treatment plans are evaluated is using "isodose lines". Radiation doses are superimposed onto 2D images (or 2D slices from the 3D CT image) of the patient using lines that show contours of equal dose. Generally, the tissue volume enclosed by an isodose line receives a dose equal to or greater than the enclosing line. The collection of isodose lines is called an "isodose distribution". Isodose lines are analogous to elevation lines on a topography map. The individual dose values of the isodose lines displayed are selected by the physician, physicist, and/or dosimetrist to best illustrate the dose coverage of the target and the dose limits of the normal tissues. The isodose distribution is examined sequentially on individual

2D cross-sectional images or image slices of the patient. Three-dimensional views of the isodose distribution are possible, but rarely used. The isodose distribution shows where dose is being delivered but gives no volumetric information, except as viewed collectively over individual slices of the 3D CT image.

56. A cumulative dose-volume histogram (CDVH or DVH) is a simple graph that concisely summarizes the volumetric information about the doses delivered to a structure volume (tumor or normal). It shows how much volume of the structure is receiving a dose equal to or greater than a specified dose. The biological response of a tumor or normal structure has been shown to correlate to the CDVH. Note that the CDVH gives no spatial information about the delivered doses, meaning it does not provide information about the dose delivered to any particular spatial location within the volume represented by the CDVH; one would look to isodose lines for that information.

57. A CDVH is constructed from the 3D pattern of dose within the patient. Each defined structure (target and normal) within the patient is represented by a set of discrete points (or voxels, defined as a volume element within a 3D image) within the structures. Voxels are analogous to pixels in a 2D image, where the pixels are points that make up or render an image. The doses at all voxels within a structure are tabulated to give partial volume data. Partial volume data generally describe what percent of a target or structure volume receives a particular dose of radiation. For example, all the points within the target usually receive a dose greater than zero. Therefore, one partial volume value for the target is that 100% of the volume has dose greater than or equal to zero. Perhaps the smallest dose in the target volume is 55 Gy. Then, 55 Gy is the "minimum dose" and 100% of the volume receives a dose of 55Gy or more. Perhaps 95% of the points have dose greater than or equal to 60 Gy and 90% of the points have doses

greater than or equal to 65 Gy. Those data represent additional partial volume values. If the largest dose value in the target is 70 Gy, then 0% of the points have doses greater than 70 Gy and 70 Gy is the "maximum dose". When all these partial volume values are plotted on a graph and connected by lines, they form a CDVH. CDVH curves of normal structures are created in the same way. Historically, and most often, CDVH curves are used to describe the dose distribution resulting from some planned arrangement of beams.

58. A CDVH curve can also be constructed from desired partial volume data. For example, a desired CDVH curve for a target volume can be made from (i) the minimum desired dose; (ii) the maximum desired dose; and (iii) the percent of the volume that should receive at least some desired goal dose. A desired constraining CDVH curve for a normal structure can be similarly constructed using partial volume data that represent tolerance doses for the structure.

59. The CDVH and isodose distribution give complementary information about a treatment plan and are used together to evaluate it. The isodose distribution shows where the dose is being received in 2-D, or in a particular slice, much like a topography map. The CDVH does not tell where in the volume the dose is being received, but rather how much of the volume is getting a particular dose.

60. There are many treatment delivery parameters that are selected during the planning process. They include the number of beams plus the direction, cross-sectional shape, dose, and intensity map (for IMRT) of each beam. The details of the delivery parameters depend on the capabilities of the treatment machine (degrees of motion, field shaping capability, energies, etc.). The term "beam geometry" typically refers to the number of beams and their directions. The orientation of a particular beam is another term for direction of the beam.

61. The original manual method of treatment planning, still used today, has been

called "forward planning". In forward planning, values for all treatment delivery parameters are selected by the planner and the resulting dose distribution is examined. Treatment parameters are repeatedly adjusted manually to improve the plan until all prescription goals are met or until no further improvement seems possible. The prescription goals are usually defined by partial volume data. The quality of the final plan depends on the skill of the treatment planner and there is no certainty that the "optimal" plan has been achieved. The treatment planning software makes no decisions about the values of delivery parameters; it computes and displays the doses that result from the decisions of the treatment planner. The quality of a plan is judged based on how close the resulting dose distribution comes to the prescription objectives.

62. Prior to the advent of IMRT, each radiation beam delivered a single dose, and computer optimization was used to find the best dose to be delivered by each beam. Although the optimization problem for IMRT is essentially the same as for non-IMRT planning, the difference is one of scale. As discussed above, each IMRT beam is subdivided into many small "beamlets," each of which has a different beam intensity, and there may be hundreds of beam intensities or beam weights for each beam.

63. During the development of IMRT, planners began using "inverse planning." In inverse planning, the user starts with the desired dose distribution and works backward ("inverse") to find the set of beam weights or intensity map for each beam that produces the desired distribution.

64. The inventor of the patent at issue in this case, Mark Carol, compared inverse planning to forward planning in an article in 1997 [Carol, 1997A]: "Because of the potential number of beams involved, and the potential range of beam weights present, treatment planning for IMRT is usually a computer-based inverse operation. Through either an iterative or an

analytic process, the beams and beam weights needed to achieve user defined goals are generated by the planning program. This is in decided contrast to the experience-based, trial-and-error approach common to conventional treatment planning where the planning software does not actually plan. Rather, it dose-simulates a user defined set of beams and beam weights." [p. 20]

D. Optimization Algorithms and Cost Functions

65. Ultimately, the goal of any computer optimization method for radiation therapy treatment planning is to find the best dose distribution for an individual patient.

66. Research on algorithms for computer optimization dates back to the late 1960's, and there is an extensive body of literature exploring the use of many optimization algorithms, including, *e.g.*, exhaustive search, linear programming, quadratic programming, mixed-integer programming, gradient search, simulated annealing, genetic algorithms, feasibility search, and neural networks.

67. Every optimization problem must have a goal. The "cost" function is the mathematical description of that goal. Every potential solution to the problem has an associated cost. The form of the cost function is independent of the optimization algorithm. However, some algorithms are limited in what cost functions they can optimize and some algorithms are more efficient for a particular cost function than others.

68. Every optimization problem also has independent parameters ("variables") that are changed to generate potential solutions to the problem. A set of values for the variables constitutes a potential solution. In radiation treatment planning, these variables are most often beam weights or intensity maps. The planned dose distribution changes as the beam weights change and, therefore, the cost changes as the beam weights change. In the process of treatment plan optimization, the beam weights (the variables) are changed, the effect on the cost value is observed, and the result is used to find a better solution.

69. The cost function and its relationship to the variables define the solution space. A solution space may have a single minimum, which means that there is one and only one best solution. This type of problem can be solved using multiple methods and all will give the same result. However, real-world problems are always more complex than this and their solution spaces have multiple minima. Each minimum is the best value within its local region and is therefore termed a "local minimum". Not all local minima are equally good.

70. The relationship between the cost function and the variables (beam weights in the case of radiation treatment planning) may be very complex. If the relationship can be written as an equation with the value of the cost on one side and the variables on the other side, then the cost function is said to be "analytic". Otherwise, the cost function is "non-analytic". Many optimization methods, such as linear programming, will not work with non-analytic cost functions.

71. Cost functions may be linear or non-linear. Linear cost functions are a particular type of analytic cost function. In a linear cost function, the equation relating the cost to the variables has only the linear operators: addition, subtraction, multiplication, and division. In a linear cost function, doubling the values of all the variables doubles the value of the cost. In other words, there is a linear relationship between the cost and the variables.

72. In contrast, in a non-linear cost function, the cost does not have a linear relationship with the variables. For example, when dose volume variables are used (such as CDVH curves), the relationship is non-linear. When the cost function is non-linear, it is susceptible to local minima and requires a certain type of optimization algorithm, a stochastic algorithm, which can escape local minima to solve the problem. See below.

73. Research into using CDVH's in treatment plan optimization goes back to the

1980's. Because CDVH's are related to normal tissue complications and are used by physicians in evaluated treatment plans, they represent a direct measure of the clinician's goals. For tumors, the critical value that represents tumor control is minimum dose. When the desired minimum tumor dose cannot be achieved, the physician looks at the volume of tumor below the minimum dose and must make a clinical judgment about how much underdose is acceptable. For normal tissues, there may be several partial volume doses that are known to correlate to poor outcome. Partial volume data that correlate to clinical responses can be extracted from the CDVH curves of dose distributions that have been demonstrated to produce those clinical results. The relationship between beam weights and CDVH is not direct. It is not possible to predict the change in a CDVH from a given change in a beam weight. The CDVH is constructed from tabulating the doses to all the points within a structure. When beam weights change, the pattern of dose within the structure changes and the doses to individual points change. Individual points that previously contributed to one part of the CDVH curve may now contribute to a different part of the curve. Only after computing the doses to all the points in the structure can the CDVH curve be created. Thus the use of CDVH parameters in a cost function makes the cost function non-linear because the relationship between the beam weights and CDVH or dose volume information cannot be predicted and the problem will be susceptible to local minima.

74. A variety of cost functions have been used in radiation therapy treatment plan optimization. In general, they have increased in complexity over time because (1) computers have increased in speed and memory permitting rapid solution to ever more difficult problems, and (2) our knowledge of the relationship between radiation dose and clinical response has improved and expanded. Early cost functions were simple mathematical functions, such as the maximum dose to the tumor, that could be easily solved using analytic or deterministic methods.

More clinically relevant cost functions that are based on CDVH's require methods such as simulated annealing.

75. Many different cost functions had been studied and were known in the art at the time of the filing of the '283 application. These included minimizing the deviation of the total dose distribution from the desired dose distribution [e.g., Webb 1989, Webb 1991A, Webb 1991B, Niemierko 1992], minimizing the deviation of the target dose from the prescription dose [e.g., Bortfeld 1993, Deasy 1997, Spirou 1998], maximizing the target dose [e.g., Morrill 1991, Rosen 1995, Langer 1996A, Langer 1996B, Deasy 1997, Yu 1997], minimizing the dose heterogeneity in the target [e.g., Niemierko 1992], minimizing the dose to normal structures [e.g., Rosen 1991], and various combinations of tumor control probability (TCP), normal tissue complication probability (NTCP), and complication-free treatment probability [e.g., Morrill 1990, Morrill 1991, Kalman 1992, Webb 1992, Mageras 1993, Deasy 1997, Webb 1997]. Constraints used in optimization at the time included minimum dose to the target [e.g., Morrill 1991], dose heterogeneity in the target [e.g., Langer 1996B], and partial volume dose limits on normal tissues [Niemierko 1992, Rosen 1995, Langer 1996A, Langer 1996B, Spirou 1998, Yu 1997].

76. Ideally, the optimization algorithm should be chosen based on the characteristics of the cost function and independent variables. When there are local minima in a problem, a stochastic algorithm that searches the solution space randomly is used. See below.

E. Optimization Algorithms: Simulated Annealing

77. Some algorithms solve the problem directly through algebraic operations. These analytic methods include linear programming and quadratic programming. These methods are unique in that they do not have multiple proposed solutions. These algorithms do not proceed iteratively from one proposed solution to another. Rather, through a series of algebraic

operations they arrive at the final optimized solution directly; there are no intermediate proposed solutions.

78. Other algorithms are non-analytic, and use a search method to solve problems. There are a variety of search methods. Some are deterministic, like grid search or gradient search. Other non-analytic algorithms are stochastic, such as simulated annealing, and genetic algorithms.

79. Non-analytic algorithms that use search methods start with an initial solution chosen by the user (or the computer). Then, they generate a new potential solution from the previous solution. This process is repeated iteratively, producing a sequence of potential solutions that converges to the best solution. Each potential solution is produced in some way by a "step" from the previous potential solution. The step is the change in the values of the variables. As the algorithm proceeds through the iterations, it gradually reduces the size of the steps so that as it gets closer to the minimum, it searches the space more finely. Such algorithms differ primarily in how they generate the steps between potential solutions.

80. Such algorithms have termination criteria. As they get closer to the minimum, they search the space more finely using smaller steps. This process can go on for a long time with improvements in the solutions getting smaller and smaller. Therefore, there is usually a termination limit selected such that when the steps get smaller than this limit or when successive improvements in the cost get less than this limit, the search is ended.

81. In deterministic algorithms that use search methods, such as grid search and gradient search, new solutions are generated based on the shape of the solution space using planned steps whose sizes and directions are intended to produce a better solution at each step. These algorithms are called deterministic because for a given problem and initial solution, these

algorithms will always repeat the same sequence of potential solutions.

82. In contrast, stochastic algorithms, such as simulated annealing, generate potential solutions using random changes in the variables. For a given problem and initial solution, these algorithms will never repeat the same sequence of potential solutions.

83. One of the major obstacles in optimization is the trapping of solutions in local minima. Deterministic search algorithms always converge to the local minimum nearest to the initial solution. These methods have no mechanism for escaping from a local region. To use them for finding the best solution in a complex solution space, the user applies them repeatedly to the problem and each time starts with a different initial solution. In this way, large areas of the solution space are explored and multiple minima can be found.

84. In contrast, stochastic algorithms can escape local minima and converge on the global minimum. Simulated annealing was developed for two reasons. The first is the need to deal with non-analytic cost functions. The second is to find the best solution in complex spaces with multiple minima. By using random steps to generate potential solutions, these algorithms can theoretically escape local regions and find the global minimum.

85. Simulated annealing was first described in the literature by Kirkpatrick in 1983. The name comes from the idea that this algorithm simulates the annealing of metals. Slow, controlled cooling of metals results in the strongest, lowest energy state crystalline structure.

86. Simulated annealing algorithms had been applied to treatment planning optimization problems for a number of years prior to the filing date of the '283 patent. *See, e.g.* Webb, Morrill, and Mohan articles.

87. Simulated annealing optimization is appealing for radiation therapy treatment planning for several reasons. It has the theoretical advantage over other algorithms of being able

to find the global minimum in a complex solution space. It is also suitable for use with virtually any cost function, even non-analytic or non-linear ones. Webb stated it eloquently: "The power of simulated annealing lies in the potentially infinite flexibility of choice of cost functions." [Webb 1997] The advantages of simulated annealing and its variants, including its relative simplicity and the fact that it was well suited for complex many-dimensional cost functions, were well known in the art prior to the filing date of the '283 patent. [CITE Morrill at p. 180]

88. Simulated annealing generates solutions by using a probability function to randomly select the step size and direction from one potential solution to the next. At each step, or iteration, of the simulated annealing algorithm, a new proposed set of beam weights is obtained by randomly adding or subtracting small grains of beam weight. [CITE Spec and Webb Articles] The proposed solution of the current iteration is compared to the accepted solution of the previous iteration. A proposed solution always becomes the best and is accepted if it has a lower cost. Occasionally, simulated annealing will accept a poorer solution as the best. Both the step size and probability of accepting a poorer solution decrease during the course of the search, similar in principle to the slow cooling of metal. As the process continues and the algorithm converges to the local minimum, the probability of escaping a local minimum becomes less and less.

89. In simulated annealing, the random nature of the step choice and the conditional acceptance of poorer solutions theoretically allow the algorithm to escape local minima. The conditional acceptance of poorer solutions is found in the published literature on simulated annealing, but it is not a defining characteristic.

90. The simulated annealing algorithm has several parameters that control its operation. First, there is a temperature parameter that determines the size of the probability

distribution from which steps are drawn. The higher the temperature parameter, the greater the steps may be. As the process continues, the temperature must be decreased and there are other parameters which control the rate of decrease ("the cooling schedule"). There are also parameters that describe the probability function itself. Finally, there are parameters that control the probability that poorer solutions will be accepted. They may or may not be linked to the temperature parameter. The values for all of these parameters are established by the user at the beginning of the optimization process and do not change. They strongly influence how rapidly simulated annealing reaching convergence and the quality of the solution. Ideally, they are "tuned" to the characteristics of the problem to be solved. Variations in simulated annealing algorithms come primarily from differences in the probability distribution and how the cooling schedule is controlled.

91. One variant of simulated annealing that was known as of the filing date of the '283 patent is fast simulated annealing (FSA), first described by Szu and Hartley in 1987 [Szu 1987]. In the 1997 publication of his talk at the 1996 Durango conference, Dr. Webb discussed the distinctions between classical simulated annealing and fast simulated annealing [Webb 1997, p. 62]. Dr. Webb explained that in fast simulated annealing, the grains of beam weight are generated by a different (Cauchy) distribution, and the cooling proceeds faster. As Dr. Webb explained, "The faster cooling and hence shorter computational times (for fast simulated annealing) are allowed because the form of the Cauchy distribution generates occasional large grains which allow the system to tunnel out of a local minimum." One skilled in the art at the time the '283 patent was filed would have appreciated that by adding occasional large grains, the treatment planning time could be shortened.

92. Webb has summarized well how simulated annealing works in radiation treatment

planning [Carol 1997]: “Iterative or stochastic methods, although slower, are able to move through a solution space (sometimes in a random manner) to find the global minimum. They are exemplified by simulated annealing which, as applied to radiation therapy treatment planning, proceeds by randomly changing beam weights, then evaluating the effect of each changed on the dose distribution. The acceptability of a change is determined by a cost function which is a mathematical quantification of how conflicting goals will be resolved; a higher cost is produced when the resulting dose distribution strays from the desired dose distribution. In general, although not always, the production of a higher cost results in throwing out of the change in beam weight (higher costs are occasionally accepted in order to allow escape from local minima). A lower cost usually results in accepting the change, and then proceeding to the next iteration. The iterative changing of beam weights continues until the cost reaches a user-designated acceptable level.”

93. Unlike analytic methods, such as linear programming algorithms, simulated annealing is an iterative method that proposes a new solution at each iteration. The simulated annealing algorithm uses a cost function to measure the cost associated with the proposed beam arrangement at each iteration to determine whether the proposed solution is better or worse than a previously accepted solution (i.e., a proposed beam arrangement accepted in a previous iteration).

Beam weight optimization in radiation therapy

94. Optimization in radiation therapy is almost exclusively focused on finding the beam weights that give the best treatment plan. Although there have been research studies on using optimization to find the best beam geometry (number of beams and directions), this problem is extremely computationally intensive.

95. In the mid 1990's, at the time of the '283 patent filing, few people in the art were attempting to optimize beam orientations (i.e., beam geometry). The optimization of beam orientations is a very complex process, and computers at that time did not have sufficient computing power to solve the geometry problem for real patients. Even today, there is little research on this problem because of the enormous computation demands.

96. In the mid-1990's, at the time the '283 patent was filed, research in this area focused in the optimization of beam weights of a given set of beams, not on the optimization of beam orientations or beam geometry.

97. Before the beam weight optimization process can begin, the treatment planner must define a set of beams for delivery. The number of beams, their directions, and other characteristics are fixed before the optimization begins. In a prelude to the optimization, the computer calculates and remembers the normalized dose to every point in the patient from each beamlet in the set of beams. Then, during optimization the dose to the patient can be quickly calculated for any set of beam weights by applying the beam weights to the normalized doses.

98. In radiation treatment planning, there are two conflicting goals. The goal for the target is a high dose to destroy the disease. At the same time, the goal for the normal tissues is a low dose to avoid radiation damage and the resulting treatment complications. Therefore, by necessity different cost functions are needed for the target and for the normal structures.

99. These conflicting goals of optimization can be implemented in one of three ways. The cost function may focus on delivering a high dose to the target and constraints are used to limit the amount of radiation to the normal tissues. The cost function may focus on minimizing the doses to the normal tissues subject to constraints that force a minimum dose to the tumor. Finally, the cost function may include doses to both the target and normal structures

and use weighting factors to drive the solution to the desired compromise.

100. When the cost function includes both target and normal tissue doses, weighting factors (importance factors) are used to quantify the relative importance of each. For example, a high relative weighting of the target cost function will drive the optimization to a solution that favors high tumor dose over low normal structure dose. Similarly, high normal tissue weightings will drive to a solution that favors sparing of the normal tissues at the expense of less dose to the target. When multiple normal structures are identified in the optimization process, each can have its own unique weighting factor because not all normal structures are equally important.

101. The inventor of the '283 patent, Mark Carol, discussed the importance of cost functions that are understandable to clinicians: "Since the cost function can be viewed as a mathematical statement of what is considered a good result, it is crucial that the user understand the specific cost function(s) employed by the planning system's optimization algorithm. Targets and structures often have different cost functions because their goals are so different." [Carol 1997A].

102. It should be understood that in the optimization process, the final result is entirely dependent on the goals specified by the user. That is, the solution is optimal only for the goals defined by user through the input parameters and importance factors entered. Changing those factors will lead to a different optimum solution.

F. The '283 Patent

103. The named inventor on the '283 patent, Mark Carol, is a clinician and founder of the NOMOS Corporation.

104. The first commercial product of the NOMOS Corporation was the Peacock system, an integrated system for the planning, delivery, and quality assurance of IMRT.

105. The treatment planning software of the Peacock system was called Peacock Plan. As described by Mark Carol, it was an inverse planning system that incorporated fast simulated annealing to optimize beam weights [Carol 1995]. Fast simulated annealing is the same variant of simulated annealing described in the specification of the '283 patent. Peacock Plan was based on the theoretical work of Dr. Steve Webb [Webb 1997].

106. Dr. Webb was a professor in the Joint Department of Physics, at the Institute of Cancer Research and Royal Marsden Hospital in Surrey, England. Dr. Webb had done seminal and significant research in the area of simulated annealing for radiation therapy treatment planning. The specification of the '283 patent states that two of Dr. Webb's articles [Webb 1989, Webb 1991] are incorporated by reference [C12, L38].

1. The Durango Conference

107. On May 17-18, 1996, Dr. Carol and NOMOS hosted the 1st NOMOS IMRT Workshop in Durango, Colorado ("the Durango Conference").

108. I attended the Durango Conference by invitation from NOMOS, along with other leading physicists and physicians in the field of radiotherapy at the time, including Dr. Steve Webb from the Institute of Cancer Research and Royal Marsden NHS Trust, Dr. Arthur Boyer from Stanford, Dr. Rock Mackie from the University of Wisconsin, Dr. Lynn Verhey from UCSF, and others.

109. Dr. Webb presented a paper at the Durango Conference concerning his work with simulated annealing in inverse treatment planning. At the conference and in the paper subsequently published, Dr. Webb explained in detail the role of simulated annealing in inverse planning for IMRT [Webb 1997]. Dr. Carol presented two papers, one on the clinically implemented PEACOCK system, and the second on the newly developed CORVUS system. I

also presented a paper at this conference on the subject of treatment planning for IMRT.

110. In the subsequent publication of the talks, Dr. Webb stated [Webb 1997] that the Peacock planning system was based on his original ideas, but that the commercial implementation of the Peacock was carried out by NOMOS.

111. In Peacock Plan, the cost function combined the deviations of the target dose from the prescribed dose and the deviations of the normal tissues doses from zero dose using a weighted sum. The inventor, Mark Carol, described it in 1997: "In PEACOCK Plan, the target cost function is the mean-squared difference between the realized dose and prescribed dose; for radiation-sensitive normal structures, the cost is the means-squared difference between realized dose and zero dose. The overall calculated cost is based on the weight assigned to each structure and target." [Carol 1997A]. This is the same cost function described by Carol in his 1995 article about Peacock [Carol 1995].

112. The CORVUS system also used inverse planning with simulated annealing, but implemented a more sophisticated cost function. Many aspects of CORVUS were presented by Dr. Carol at the Durango Workshop, which I attended, and in the published proceedings [Carol 1997A]. A more detailed description of the CORVUS cost function was described by Dr. Carol in the proceedings of the XIIth International Conference on the Use of Computers in Radiation Therapy [Carol 1997C]. The cost function utilized in the CORVUS system as described by Dr. Carol in 1997 was virtually identical to the cost function claimed in the '283 patent.

113. The cost function in CORVUS was constructed using CDVH's: "An interface has been implemented that supports the entry of partial volume information for each structure, out of which cumulative dose volume histogram curves are generated and used as the goal by the

optimizer." [Carol 1997C] The '283 patent states that the CDVH "may be entered graphically into the computer" or that it may be constructed from partial volume data entered by the user [C5, L5]. However, the patent also states that "in the system of the present invention, partial volume data are entered by the user during the Prescription Panel step ..." [C10, L56]. This approach is the same as described by Dr. Carol in 1997 [Carol 1997B, Carol 1997C].

114. In his description of CORVUS, Dr. Carol writes "After a CDVH is constructed from user-entered partial volume values, the system divides the CDVH into regions and automatically assigns a relative weight to each." [Carol 1997B, Carol 1997C] This operation is similar to the regions or zones identified in the patent in Figures 3 and 4 [C12, L48]. As in the description of CORVUS, the patent states that "Relatives weights are then assigned by the computer ..." The description of the CORVUS zones by Dr. Carol in 1997 is virtually identical to the zones described in the patent [Carol 1997C].

2. Claims 25 and 29 of the '283 Patent

115. Claims 25 and 29 of the '238 patent are directed to a computer that runs a simulated annealing algorithm to determine an optimized radiation treatment plan for delivery to the patient. Claims 25 and 29 of the '283 patent are directed specifically to the optimization of beam weights. The claims do not address optimization of beam geometry.

116. Beam weights, although related to dose, are not equivalent to dose. Beam weight, or beam intensity, refers to the radiation that is emitted from beamlets of a beam at the source, the linear accelerator (as discussed above). Dose, on the other hand, refers to the radiation that is absorbed by the tissue.

117. The patent describes existing methods for delivering conformal treatments. It does not claim a new conformal radiation therapy apparatus.

118. In the "SUMMARY OF INVENTION", the patent describes a methodology to be implemented on a computer for determining the optimum intensity maps for an IMRT treatment. It further states that the resulting optimized radiation beam arrangement should be capable of delivery with a conformal radiation therapy apparatus [C8, L14].

119. One skilled in the art at the time that the '283 patent was filed would understand that, in order to computationally obtain a proposed array of beam weights, a computer would have to be configured with and run treatment planning optimization software, including a specific optimization algorithm.

120. There are essentially three components to the inverse planning method presented in the patent: the computer configured to run an optimization algorithm for finding the optimum beam weights [e.g., C7, L11-L25], the method of user definition of the treatment planning goals [e.g., Figure 5, C10, L53 - C11, L8], and the cost function that mathematically describes the goal of optimization [e.g., C13, L10-39, Figure 3 and 4].

121. Dr. Webb's 1989 article, incorporated by reference in the specification of the '283 patent, explains that the simulated annealing algorithm is used to obtain a proposed set of beam weights. The specification of the '283 patent does not describe how the proposed set of beam weight is obtained, other than by reference to Dr. Webb's articles. [Webb 1989]

122. Neither the '283 patent specification nor Dr. Webb's articles disclose any way to obtain a proposed set of beam weights for IMRT other than through simulated annealing.

123. The use of simulated annealing to calculate a proposed radiation beam arrangement was well known in the art prior to the time of the patent filing, and the patent acknowledges that [C8, L61]. At each iteration of the simulated annealing algorithm, a new proposed set of beam weights is obtained by randomly adding or subtracting small grains (or

amounts) of beam weight. [Webb 1989] By changing the beam weights at a particular iteration, a new proposed radiation beam arrangement or new set or array of beam weights is created. The change of beam weights at a particular iteration results in a new proposed radiation beam arrangement, which is the new proposed solution for that iteration. The concept of proposing a new solution at each iteration is consistent with optimization algorithms such as simulated annealing.

124. One skilled in the art would have understood that the cost function claimed in the ‘283 patent is the specific cost function described in Column 13, in light of the specification, the Webb articles, and knowledge and experience in the field. One skilled in the art would not have understood the claimed cost function to encompass any cost function, because it was well known that a variety of cost functions had been used with variants of the simulated annealing algorithm (and with other algorithms) to optimize beam weights prior to the filing date of the ‘283 application.

125. The specific cost function described in Column 13 of the ‘283 patent was a “non-linear” cost function and was designed to solve a particular problem. The cost function is non-linear because it incorporates partial volume data or CDVH parameters into the cost function.

126. The specification teaches that the cost function of the ‘283 patent is incorporated into the simulated annealing algorithm. The specification does not teach how to use this cost function with any optimization algorithm other than simulated annealing.

127. In my opinion, one of ordinary skill in the art at that time would have appreciated that it would have required additional experimentation for one skilled in the art to determine how to use the cost function of the ‘283 patent with an algorithm other than simulated

annealing. Indeed, it would not have been a trivial exercise to attempt to use an algorithm other than simulated annealing with this cost function.

128. Given that there is no disclosure of any optimization algorithm other than simulated annealing (and its variants, such as fast simulated annealing) in the '283 patent or the Webb articles, and that it would have been difficult to figure out a way to use the cost function of the '283 patent with any algorithm other than simulated annealing, one skilled in the art would understand that claims 25 and 29 are limited to a computer that runs a simulated annealing algorithm. Moreover, one of skill in the art would recognize that a stochastic algorithm such as simulated annealing would be required with such a cost function.

129. In a publication contemporaneous with the filing of the '283 patent, Dr. Carol explained the meaning of the phrase "changing the proposed radiation beam arrangement iteratively." Dr. Carol explained: "The iterative approach to solving the optimization problem involves iteratively changing the strengths of the individual beamlets until a satisfactory solution is achieved." [Carol 1997C, p. 317]

130. In my opinion, the skilled artisan at the time the '283 patent application was filed would have appreciated that the "partial volume data associated with the predetermined desired dose prescription" referred to the partial volume data for each target and structure entered into the prescription panel by the user before the optimization, based on the desired dose prescription of the physician. Such partial volume data were used to generate a CDVH curve for each target and structure that represented the desired dose prescribed by the physician.

131. The skilled artisan would have appreciated that the total cost of the claimed cost function could not be calculated without referring to the CDVH's because the cost formulas depend on the zones of the CDVH curves, and the weighting factors for each of the zones.

132. The skilled artisan would have appreciated that the cost function compares the CDVH associated with the predetermined desired dose prescription with the CDVH's associated with the proposed radiation beam arrangement at each iteration of the simulated annealing algorithm and calculates a cost.

133. The cost function calculates the total cost of the proposed array of beam weights at a particular iteration of the simulated annealing algorithm based on the formulas disclosed in Column 13 of the '283 patent. This number itself does not mean much; it is an abstract concept and does not indicate whether the proposed solution is a good solution. Only by comparing the total cost of proposed beam weight solution of the given iteration to the cost of the proposed beam weight solution of the previous iteration, can one tell whether the solution is better or worse. This comparison of costs is implicit in the terms "greater correspondence" or "lesser correspondence" found in the last "accept or reject" limitation of the asserted claims.

134. One skilled in the art at the time the '283 patent was filed would understand that the simulated annealing algorithm would reject the new proposed array of beam weights if the total cost was higher than the total cost of the accepted proposed solution of the previous iteration, and would accept the new proposed array of beam weights if the total cost was lower than the total cost of the accepted proposed solution of the previous iteration. Practically speaking, the comparison must be between the proposed solution of the current iteration and the last accepted solution of a previous iteration. If the solution of the immediately preceding iteration was rejected, it would not have been available as a comparator.

I declare under penalty of perjury under the laws of the United States of

America that the foregoing is true and correct, and if called to testify on the foregoing I could and would testify competently thereto.

Dated March 29, 2012



Isaac I. Rosen, Ph.D.

EXHIBIT 1

Curriculum Vitae

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2006-2008 Adjunct Professor

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1993-1999 Associate Professor (tenured) and Associate Physicist

2002-2004 Section Chief, Core Services Group

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1999 Fellow, American Association of Physicists in Medicine

Licensure and Board Certifications

1993 Texas Board of Licensure for Professional Medical Physics, License number 0101
 1991 American Board of Medical Physics, Radiation Oncology Physics
 1980 American Board of Radiology, Therapeutic Radiological Physics

Funded Research

2004-2005 Co-Principal Investigator, "On Line Verification of Dose Delivery Using MarkerVision," Varian Medical Systems, \$59,000 (total cost).
 2001-2005 Principal Investigator, "Radiation Therapy Treatment Planning," ADAC Laboratories, \$626,375 (total costs).
 1998-2000 Co-Principal Investigator, "Radiation Therapy Treatment Planning." ADAC Laboratories, \$262,390 (total costs).
 1997-1998 Principal Investigator, "Radiation Therapy Dose Escalation for the Prostate Using Intensity-Modulated Beams." The University of Texas M. D. Anderson Cancer Center Physician Referral Service, \$44,340.
 1996-1997 Principal Investigator, "Radiotherapy PACS Research." IMPAC sponsored research agreement, \$85,556.
 1995-1996 Co-investigator, "Radiotherapy Treatment Planning System Research." General Electric research agreement, \$162,660.
 1992-1993 Principal Investigator, "Experimental Evaluation of Segmented Conformal Radiation Therapy." Houston Institute for Cancer Research, Detection and Treatment, \$35,000 (direct costs).
 1991-1994 Co-investigator, "Mathematical Programming of Radiotherapy Plans." The Whitaker Foundation, \$180,000 (direct costs).
 1990-1991 Principal Investigator, "Monte Carlo Studies of Ionization Chamber Design." Cray Research, Inc., \$7,400.
 1988-1995 Principal Investigator, "Conformal Radiation Therapy Treatment Plan Optimization." National Cancer Institute R01-CA46634, \$1,004,000 (total costs).

Teaching

Louisiana State University/Mary Bird Perkins Cancer Center, Baton Rouge, LA
 2006-2007 Adjunct Professor
 2006-2007 Served on 3 graduate supervisory committees, chaired 2
 2006-2007 Supervised 1 post-doctoral fellow

The University of Texas Graduate School of Biomedical Sciences, Houston, TX

2005-2005 Instructor, "Mathematics for Medical Physics"
 2002-2004 Instructor, Department of Radiation Physics Short Course, "IMRT"
 1998-2001 Membership Committee
 1996-2001 Instructor, Department of Radiation Physics Short Course, "Dosimetry of High Energy Electron and X-Ray Therapy Machines"
 1995-2003 Coordinator and instructor, "Anatomy and Oncology for Medical Physicists"
 1996-2004 Instructor, "Introductory Radiation Therapy Physics Rotation"
 1995-1998 Medical Physics Program Steering Committee
 1993-1999 Instructor, "Mathematics for Medical Physics"
 1994-2001 Supervised 5 tutorials
 1995-2003 Served on 15 graduate advisory committee, chaired 6
 1993-2012 Served on 17 graduate supervisory committees, chaired 5
 1998-1999 Supervised 1 post-doctoral fellow

The University of Texas Medical Branch, Galveston, TX

1986-1990 Lecturer, medical school students
 1983-1993 Lecturer, radiotherapy resident training program
 1989-1992 Supervised 2 post-doctoral students

Institutional Service (Selected)

The University of Texas M.D. Anderson Cancer Center, Department of Radiation Physics, Houston, Texas
 2004-2005 MDACC Credentials Committee of the Medical Staff (CCMS)
 2002-2004 MDACC Clinical Faculty Review Committee (CFRC)
 1995-2003 Division of Radiation Oncology, Promotions and Tenure Committee
 1994-2000 MDACC Faculty Senate

Professional Service (Selected)

2004-2006 American Association of Physicists in Medicine, Work Group on IMRT
 2004-2005 AAPM representative to the ASTO IHE-RO Task Force
 2000-2004 American Association of Physicists in Medicine, IMRT Subcommittee
 2002-2003 International Journal Radiation Oncology, Biology, Physics, Ad Hoc Associate Editor
 2001-2003 American Society for Therapeutic Radiology and Oncology, annual meeting and program committee
 2001-2004 American Association of Physicists in Medicine, Molecular Imaging in Clinical Radiation Oncology Subcommittee
 2000-2002 Radiation Therapy Oncology Group, Medical Physics Committee
 2000-2002 American Association of Physicists in Medicine, Radiation Therapy Committee
 2000-2001 Marconi Oncology Systems Advisory Board
 2000-2000 American Association of Physicists in Medicine, Ad Hoc Working Group on biological and functional imaging in radiation therapy, Chair
 1993-1995 American Association of Physicists in Medicine, Finance Committee
 1990-1991 American College of Radiology, Committee on Radiation Oncology Physics
 1990-1994 American College of Radiology, Commission on Radiation Oncology, US Technical Advisory Group to the International Electrotechnical Commission
 1989-1989 American Association of Physicists in Medicine, Task Group 1, "Role of the Physicist in Radiation Oncology"
 1988-1990 American Association of Physicists in Medicine, Task Group 4, "Quality Assurance in Medical Computer Systems"
 1987-1989 American Association of Physicists in Medicine, Task Group 35, "Accelerator Safety"
 1987-1989 American Association of Physicists in Medicine, Task Group, "Artificial Intelligence"
 1987-1987 American Association of Physicists in Medicine, organized and hosted the 4th Annual Software Exchange Workshop, Galveston, TX
 1979-1983 American Association of Physicists in Medicine, Board of Directors

Membership in Scientific and Professional Societies

1991-2011 American College of Medical Physics
 1991- American College of Radiology
 1988- American Society for Radiation Oncology
 1984- American Association for Computing Machinery
 1976- American Association of Physicists in Medicine

Session Chair at National and International Conferences

2006 American Association of Physicists in Medicine, 48th annual meeting, Scientific Session MO-E224C, "Teletherapy planning and delivery I", Orlando, FL.
 2003 American Association of Physicists in Medicine, 45th annual meeting, Scientific Session TU-C20B, "IMRT: Planning and Optimization", San Diego, CA
 2001 American Society for Therapeutic Radiology and Oncology, 43th annual meeting, Scientific Session Y, Physics IV, "Treatment Planning and Evaluation", San Francisco, CA
 2000 World Congress on Medical Physics and Biomedical Engineering, Scientific Session MO-B309, "Optimization 1", Chicago, IL
 1999 International Symposium 3-D Conformal Radiation Therapy and Intensity Modulated Radiation Therapy in the New Millennium, Session IV, "Treatment Plan Optimization", Houston, TX
 1998 Radiological Society of North America, 84th annual meeting, Scientific Session "Radiation Oncology (Radiation Physics, Biology)", Chicago, IL
 1996 American Association of Physicist in Medicine, 38th annual meeting, Scientific Session WE-D1, "Treatment Planning", Philadelphia, PA
 1994 American Association of Physicist in Medicine, 36th annual meeting, Scientific Session O, "Therapy: Treatment Planning and Delivery", Anaheim, CA
 1993 American Society for Therapeutic Radiology and Oncology, 35th annual meeting, Scientific Session X, "Dynamic Therapy", New Orleans, LA
 1993 American Association of Physicist in Medicine, 35th annual meeting, Scientific Session G, "Therapy: Dosimetry: Wedges", Washington DC

Refereed Publications

1. AR Smith, II Rosen, KR Hogstrom, HM Prichard, "The silicon P-I-N Diode as an in vivo dosimeter for fast neutrons," *Int. J. Rad. Onc. Biol. Phys.* 2, 111-116 (1977).
2. MD Stevens, II Rosen, RG Lane, "Satellite digital display for the Clinac 18," *Med. Phys.* 4, 454-455 (1977).
3. AR Smith, II Rosen, KR Hogstrom, RG Lane, CA Kelsey, HI Amols, C Richman, PA Berardo, JA Helland, RS Kittell, MA Paciotti, NJ Bradbury, "Dosimetry of pion beams," *Med. Phys.* 4, 408-413 (1977).
4. RT Park, II Rosen, "A self-consistent N/D calculation of the rho meson using the Veneziano model," *Acta Physica Polonica B8*, 549-555 (1977).
5. RG Lane, D Lake, II Rosen, CA Kelsey, "A whole body repositioning system," *Radiology* 126, 258-259 (1978).
6. II Rosen, A Smith, R Lane, C Kelsey, D Lake, K Hogstrom, J Somers, J Helland, R Kittel, H Amols, J Bradbury, C Richman, "An automated dosimetry data acquisition and analysis system at LAMPF Pion Radiotherapy Facility," *Med. Phys.* 5, 120-123 (1978).
7. KR Hogstrom, AR Smith, JW Somers, RG Lane, II Rosen, SL Simon, CA Kelsey, "Measurement of the effect of inhomogeneities and compensating bolus in clinical pion beams," *Med. Phys.* 6, 26-31 (1979).
8. J Somers, KR Hogstrom, RT Slice, II Rosen, AR Smith, "A multi-channel electrometer data acquisition system," *IEEE Trans. Nuc. Sci.* NS-26, 4596-4600 (1979).
9. KR Hogstrom, AR Smith, SL Simon, JW Somers, RG Lane, II Rosen, CA Kelsey, CF Von Essen, MM Kligerman, PA Berardo, SM Zink, "Static pion beam treatment planning of deep seated tumors using computerized tomographic scans at LAMPF," *Int. J. Rad. Onc. Biol. Phys.* 5, 875-886 (1979).
10. II Rosen, MD Stevens, JW Somers, RG Lane, CA Kelsey, "Computer interface for a linear accelerator," *Med. Phys.* 7, 68-69 (1980).
11. II Rosen, RG Lane, CA Kelsey, "Accuracy of a two sensor sonic digitizer," *Med. Phys.* 6, 536-538 (1979).
12. II Rosen, RG Lane, CA Kelsey, "Computation of dose distributions for radioactive seed implants," *Acta Radiol. Onc.* 19, 41-44 (1980).
13. KR Hogstrom, II Rosen, "Diffusion rates of positron emitters in pion irradiated patients," *Phys. Med. Biol.* 25, 927-932 (1980).
14. KR Hogstrom, II Rosen, E Gelfand, "Calculation of pion dose distributions in water," *Med. Phys.* 7, 703-709 (1980).
15. II Rosen, TC Hall, F Mettler, J Wicks, CA Kelsey, DE Gustafson, "A computerized database system from medical diagnostic studies (DIASTU)," *Comp. Prog. Biomed.* 12, 249-261 (1980).
16. HI Amols, II Rosen, "A three-film technique for reconstruction of radioactive seed implants," *Med. Phys.* 8, 210-214 (1981).
17. II Rosen, KM Khan, RG Lane, CA Kelsey, "The effect of geometric errors in the reconstruction of iridium-192 seed implants," *Med. Phys.* 9, 222-223 (1982).
18. II Rosen, RG Lane, HL Van Camp, "An equivalent squares template," *Med. Phys.* 10, 892-894 (1983).
19. II Rosen, "Isodose plotting for pen plotters," *Med. Phys.* 12, 649-651 (1985).
20. II Rosen, W Gordon, MD Loyd, "A surface mold using iridium-192 seeds," *Int. J. Rad. Onc. Biol. Phys.* 12, 203-2207 (1986).
21. MD Loyd, RG Lane, J Laxton, CH Chow, II Rosen, "Longterm variation in beam symmetry as a function of gantry angle for a computer-controlled linear accelerator," *Med. Phys.* 16, 614-617 (1989).
22. M Loyd, H Chow, J Laxton, I Rosen, R Lane, "Dose delivery error detection by a computer-controlled linear accelerator," *Med. Phys.* 16, 137-139 (1989).
23. II Rosen, RG Lane, "Positional accuracy of isodose lines as a function of dose matrix resolution," *Phys. Med. Biol.* 35, 423-427 (1990).
24. II Rosen, MD Loyd, RG Lane, "Collimator scatter in modeling radiation beam profiles," *Med. Phys.* 17, 422-428 (1990).
25. SM Morrill, II Rosen, RG Lane, JA Belli, "The Influence of dose constraint point placement on optimized radiation therapy treatment planning," *Int. J. Rad. Onc. Biol. Phys.* 19, 129-141 (1990).
26. RG Lane, MD Loyd, CH Chow, E Ekwelundu, II Rosen, "Improved dose homogeneity in the head and neck using computer controlled radiation therapy," *Int. J. Rad. Onc. Biol. Phys.* 19, 1531-1538 (1990).
27. CH Chow, RG Lane, II Rosen, "Uncertainty in dose estimation for gynecological implants," *Int. J. Rad. Onc. Biol. Phys.* 19, 1555-1559 (1990).
28. SM Morrill, RG Lane, II Rosen, "Constrained simulated annealing for optimized radiation therapy treatment planning," *Comp. Prog. Biomed.* 33, 135-144 (1990).
29. II Rosen, RG Lane, SM Morrill, JA Belli, "Treatment plan optimization using linear programming," *Med. Phys.* 18, 141-152 (1991).
30. SM Morrill, RG Lane, G Jacobson, II Rosen, "Treatment planning optimization using constrained simulated annealing," *Phys. Med. Biol.* 36, 1341-1361 (1991).
31. SM Morrill, RG Lane, JA Wong, II Rosen, "Dose-volume considerations with linear programming optimization," *Med. Phys.* 18, 1201-1210 (1991).

32. RG Lane, MD Loyd, CH Chow, E Ekwelundu, II Rosen, "Custom beam profiles in computer-controlled radiation therapy," *Int. J. Rad. Onc. Biol. Phys.* 22, 167-174 (1992).
33. II Rosen, SM Morrill, RG Lane, "Optimized dynamic rotation with wedges," *Med. Phys.* 19, 971-977 (1992).
34. AS Zacarias, RG Lane, II Rosen, "Assessment of a linear accelerator for segmented conformal radiation therapy," *Med. Phys.* 20, 193-198 (1993).
35. JA Purdy, PJ Biggs, C Bowers, E Dally, W Downs, BA Fraass, CJ arzmark, F Khan, P Morgan, R Morton, J Palta, II Rosen, T Thorson, G Svensson, J Ting, "Medical accelerator safety considerations: Report of the AAPM Radiation Therapy Committee Task Group No. 35," *Med. Phys.* 20, 1261-1275 (1993).
36. SM Morrill, ML Langer, RG Lane, II Rosen, "Tissue heterogeneity effects in treatment plan optimization," *Int. J. Rad. Onc. Biol. Phys.* 30, 699-706 (1994).
37. SM Morrill, KS Lam, RG Lane, M Langer, II Rosen, "Very fast simulated reannealing in radiation therapy treatment plan optimization," *Int. J. Rad. Onc. Biol. Phys.* 31, 179-188 (1995).
38. II Rosen, KS Lam, RG Lane, M Langer, SM Morrill, "Comparison of simulated annealing algorithms for conformal therapy treatment planning," *Int. J. Rad. Oncol. Biol. Phys.* 33(5), 1091-1099 (1995).
39. A Pollack, GK Zagars, G Starkschall, CH Childress, S Kopplin, AL Boyer, II Rosen, "Conventional versus conformal radiotherapy for prostate cancer: Preliminary results of dosimetry and acute toxicity," *Int. J. Rad. Onc. Biol. Phys.* 34, 555-564 (1996).
40. TR Willoughby, G Starkschall, NA Janjan, II Rosen, "Evaluation and scoring of radiotherapy treatment plans using an artificial neural network," *Int. J. Rad. Onc. Biol. Phys.* 34, 921-930 (1996).
41. II Rosen, "Writing Software for the Clinic," *Med. Phys.* 25(3), 1-9 (1998).
42. J Britt, II Rosen, "A comparison of measured and calculated output for highly blocked photon fields," *Medical Dosimetry* 23(1), 51-55 (1998).
43. JA Antolak, II Rosen, CH Childress, GK Zagars, A Pollack, "Prostate target volume variations during a course of radiotherapy," *Int. J. Rad. Onc. Biol. Phys.* 42(3), 661-672 (1998).
44. RA Boyd, KR Hogstrom, II Rosen, "Effect of using an initial polyenergetic spectrum with the pencil-beam redefinition algorithm for electron-dose calculations in water," *Med. Phys.* 25(11), 2176-2185 (1998).
45. JA Antolak, II Rosen, "Planning target volumes for radiotherapy: How much margin is needed?" *Int. J. Rad. Onc. Biol. Phys.* 44(5), 1165-1170 (1999).
46. AM Steadham, HH Liu, CH Crane, NA Janjan, II Rosen, "Optimization of beam orientations and weights for coplanar conformal beams in treating pancreatic cancer," *Med. Dosimetry* 24(4), 265-271 (1999).
47. A Pollack, GK Zagars, II Rosen, "Prostate cancer treatment with radiotherapy: Maturing methods that minimize morbidity," *Seminars in Oncology* 26(2), 150-161 (1999).
48. G Starkschall, RE Steadham, RA Popple, S Ahmad, II Rosen, "Beam commissioning methodology for a 3-D convolution/superposition photon dose algorithm," *J. Applied Clin. Med. Physics* 1(1), 8-27 (2000).
49. G Starkschall, RE Steadham, NH Wells, L O'Neill, LA Miller, II Rosen, "On the need for monitor unit calculations as part of a beam commissioning methodology for a radiation treatment planning system," *J. Applied Clin. Med. Physics* 1(3), 86-94 (2000).
50. MR Storey, A Pollack, G Zagars, L Smith, J Antolak, I Rosen, "Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial," *Int J Rad Onc Biol Phys* 48(3):635-642 (2000).
51. A Pollack, GK Zagars, LG Smith, JJ Lee, AC von Eschenbach, JA Antolak, G Starkschall, I Rosen, "Preliminary Results of a Randomized Radiotherapy Dose-Escalation Study Comparing 70 Gy with 78 Gy for Prostate Cancer," *J Clin Oncol* 18(23):3904-3911 (2000).
52. HH Liu, II Rosen, NA Janjan, A Pollack, "Treatment planning optimization based on response-surface modeling of cost function versus multiple constraints," CD-ROM Proceedings of the 2000 World Congress on Medical Physics and Biomedical Engineering, 4 pp, July 23-28, Chicago (2000).
53. G Starkschall, RE Steadham, NH Wells, L O'Neill, LA Miller, II Rosen, "Monitor unit calculations as part of beam commissioning for a radiation treatment planning system," CD-ROM Proceedings of the 2000 World Congress on Medical Physics and Biomedical Engineering, 4 pp, July 23-28, Chicago (2000).
54. II Rosen, TA Fischer, JA Antolak, G Starkschall, EL Travis, SL Tucker, KR Hogstrom, JD Cox, R Komaki, "Correlation between lung fibrosis and radiation therapy dose following concurrent radiation therapy and chemotherapy for limited small-cell lung cancer," *Radiology* 221(3):614-622 (2001).
55. CH Crane, JA Antolak, II Rosen, KM Forster, DB Evans, NA Janjan, C Charnsangavej, PW Pisters, R Lenzi, MA Papagikos, RA Wolff, "Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head," *Int J Gastrointest Cancer* 30(3):123-32 (2001).
56. MT Gillin, J Galvin, IA Brezovich, J Chu, I Das, NA Detorie, D Fontenla, W Hanson, WB Harms Sr, MS Huq, R Kline, C Orton, EB Podgorsak, J Purdy, I Rosen, M Schell, N Suntharalingam, KA Winter, JK De Wyngaert, "Radiation Therapy

Oncology Group. Research Plan 2002-2006. Medical Physics Committee." *Int J Radiat Oncol Biol Phys.* 51(3 Suppl 2):96-102 (2001).

57. E Huang, L Dong, A Chandra, DA Kuban, II Rosen, A Evans, A Pollack, "Intrafraction prostate motion during IMRT for prostate cancer," *Int J Rad Onc Biol Phys* 53(2):261-268 (2002).

58. NL Childress, L Dong, I Rosen, "Rapid radiographic field calibration for IMRT verification using automated MLC fields," *Medical Physics* 29(10):2384-2390 (2002).

59. A Pollack, GK Zagars, G Starkschall, JA Antolak, JJ Lee, E Huang, AC von Eschenbach, DA Kuban, I Rosen, "Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial," *Int J Rad Onc Biol Phys* 53(5):1097-1105 (2002).

60. E Huang, A Pollack, L Levy, G Starkschall, L Dong, I Rosen and DA Kuban, "Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer," *Int J Rad Onc Biol Phys* 54(5):1314-1321 (2002).

61. A Pollack, GK Zagars, JA Antolak, DA Kuban and II Rosen, "Prostate biopsy status and PSA nadir level as early surrogates for treatment failure: analysis of a prostate cancer randomized radiation dose escalation trial," *Int J Rad Onc Biol Phys* 54(3):677-685 (2002).

62. A Chandra, L Dong, E Huang, DA Kuban, L O'Neill, I Rosen, A Pollack, "Experience of ultrasound-based daily prostate localization," *Int J Rad Onc Biol Phys* 56(2):436-447 (2003).

63. L Dong, J Antolak, M Salehpour, K Forster, L O'Neill, R Kendall, I Rosen, "Patient-specific point dose measurement for IMRT monitor unit verification," *Int J Rad Onc Biol Phys* 56(3):867-877 (2003).

64. NL Childress, II Rosen, "The design and testing of novel clinical parameters for dose comparison", *Int J Rad Onc Biol Phys* 56(5):1464-1479 (2003).

65. L Court, I Rosen, R Mohan, L Dong, "Evaluation of mechanical precision and alignment uncertainties for an integrated CT/LINAC system", *Med Phys* 30(6):1198-1210 (2003).

66. WD D'Souza, II Rosen, "Non-tumor integral dose in conformal radiotherapy treatment planning," *Med Phys* 30(8):2065-2071 (2003).

67. GA Ezzell, JM Galvin, D Low, JR Palta, I Rosen, MB Sharpe, P Xia, Y Xiao, L Xing, CX Yu, "Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM radiation therapy committee," *Med Phys* 30(8):2089-2115 (2003).

68. D Kuban, A Pollack, E Huang, L Levy, L Dong, G Starkschall, I Rosen, "Hazards of dose escalation in prostate cancer radiotherapy," *Int J Rad Onc Biol Phys* 57(5):1260-1268 (2003).

69. JC O'Daniel, L Dong, DA Kuban, H Liu, N Schechter, S Tucker, I Rosen, "The delivery of IMRT with a single physical modulator for multiple fields: a feasibility study for paranasal sinus cancer," *Int J Rad Onc Biol Phys* 58(3):876-887 (2004).

70. JM Galvin, G Ezzell, A Eisbrauch, C Yu, B Butler, Y Xiao, I Rosen, J Rosenman, M Sharpe, L Xing, P Xia, T Lomax, DA Low, J Palta, "Implementing IMRT in clinical practice," *Int J Rad Onc Biol Phys* 58(5):1616-1634 (2004).

71. U Selek, R Cheung, M Lii, P Allen, RE Steadham, TR Vantreese, DJ Little, II Rosen, D Kuban, "Erectile dysfunction and radiation dose to penile base structures after prostate cancer radiotherapy: a lack of correlation," *Int J Rad Onc Biol Phys* 59:1039-1046 (2004).

72. NL Childress, II Rosen, "Effect of processing time delay on the dose response of Kodak EDR2 film," *Med Phys* 31(8):2284-2288 (2004).

73. I Rosen, HH Liu, N Childress, Z Liao, "Interactively exploring optimized treatment plans," *Int J Rad Onc Biol Phys* 61:570-582 (2005).

74. NL Childress, C Bloch, RA White, M Salehpour, II Rosen, "Detection of IMRT delivery errors using a quantitative 2D dosimetric verification system." *Med Phys* 32(1):153-162 (2005).

75. NL Childress, M Salehpour, L Dong, C Bloch, RA White, II Rosen, "Dosimetric accuracy of Kodak EDR2 film for IMRT verifications." *Med Phys* 32(2):539-548 (2005).

76. SF Kry, M Salehpour, DS Followill, M Stovall, DA Kuban, RA White, II Rosen, "The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy," *Int J Rad Onc Biol Phys* 62:1195-1203 (2005).

77. SF Kry, M Salehpour, DS Followill, M Stovall, DA Kuban, RA White, II Rosen, "Out-of-field photon and neutron dose equivalents from step-and-shoot intensity-modulated radiation therapy," *Int J Rad Onc Biol Phys* 62:1204-1216 (2005).

78. NL Childress, RA White, C Bloch, M Salehpour, L Dong, II Rosen, "Retrospective analysis of 2D patient-specific IMRT verifications," *Med Phys* 32(4):838-850 (2005).

79. B Dabaja, MR Salehpour, I Rosen, S Tung, WH Morrison, KK Ang, AS Garden, "Intensity modulated radiation therapy (IMRT) of cancers of the head and neck: comparison of split-field and whole-field techniques," *Int J Rad Onc Biol Phys* 63(4):1000-1005 (2005).

80. HH Liu, P Balter, T Tutt, B Choi, J Zhang, C Wang, M Chi, D Luo, T Pan, S Hunjan, G Starkschall, I Rosen, K Prado, Z Liao, J Chang, R Komaki, JD Cox, R Mohan, L Dong, "Assessing respiration-induced tumor motion and internal target volume using four-dimensional computed tomography for radiotherapy of lung cancer," *Int J Rad Onc Biol Phys* 68(2):531-540 (2007).

81. TK Lee, II Rosen, JP Gibbons, RS Fields, KR Hogstrom, "Helical tomotherapy for parotid gland tumors," *Int J Rad Onc Biol Phys* 70(3):883-891 (2008).
82. D Cheek, JP Gibbons, II Rosen, KR Hogstrom, "Accuracy of TomoTherapy treatments for superficial target volumes," *Med Phys* 35(8):3565-3573 (2008).
83. S Hunjan, G Starkschall, I Rosen, K Prado, N Tolani, P Balter, "Comparison of breath-hold and free-breathing positions of an external fiducial analysis of respiratory traces," *J App Clin Med Phys* 9(3):34-42 (2008).
84. AB Beardmore, II Rosen, DA Cheek, RS Fields, KR Hogstrom, "Evaluation of MVCT images with skin collimation for electron beam treatment planning," *J App Clin Med Phys* 9(3):43-57 (2008).
85. JP Gibbons, K Smith, D Cheek, I Rosen, "Independent calculation of dose from a helical TomoTherapy unit," *J App Clin Med Phys* 10(1):103-119 (2009)
86. M Ashenafi, RA Boyd, TK Lee, KK Lo, JP Gibbons, II Rosen, JD Fontenot, KR Hogstrom, "Feasibility of post-mastectomy treatment with helical tomotherapy," *Int J Rad Onc Biol Phys* 77(3):836-842 (2010).
87. JE Matney, BC Parker, DW Neck, G Henkelmann, II Rosen, "Evaluation of a commercial flatbed document scanner and radiographic film scanner for radiochromic EBT film dosimetry," *J App Clin Med Phys* 11(2):198-208 (2010).
88. JE Matney, BC Parker, DW Neck, G Henkelmann, II Rosen, "Target localization accuracy in a respiratory phantom using BrainLab ExacTrac and 4DCT imaging," *J App Clin Med Phys* 12(2):301-309 (2011).
89. M Moldovan, JD Fontenot, JP Gibbons, TK Lee, II Rosen, RS Fields, KR Hogstrom, "Investigation of pitch and jaw width to decrease delivery time of helical tomotherapy treatments for head and neck cancer," *Med Dos* 36(4):397-403 (2011).

Book Chapters

1. II Rosen, KM Rowinski, "Models for Iridium-192 Seed Implants," *Proceedings of the Eighth International Conference on the Use of Computers in Radiation Therapy*, IEEE Computer Society Press, Silver Springs, MD 354-358 (1984).
2. II Rosen, RG Lane, "Treatment Plan Optimization for Conformal Therapy," *Proceedings of the Ninth International Conference on the Use of Computers in Radiation Therapy*, Elsevier Science Publishers BV, The Netherlands, 357-360 (1987).
3. T Blake, PA Hickling, RG Lane, AE Nahum, II Rosen, ME Rosenbloom, "Assessment of the Philips SL25 Linac for Conformation Therapy," *Proceedings of the Ninth International Conference on the Use of Computers in Radiation Therapy*, Elsevier Science Publishers BV, The Netherlands, 537-540 (1987).
4. RG Lane, CH Chow, MD Loyd, JL Laxton, II Rosen, "One Perspective of Quality Assurance in Radiation Therapy," in *Quality Assurance in Radiotherapy Physics*, (Medical Physics Publishing Corporation, Madison, 1991).
5. RG Lane, II Rosen, JA Belli, "Development of Computer-Controlled Radiation Therapy at the University of Texas Medical Branch," *Proceedings of the Philips Radiotherapy Users Meeting* (1992).
6. II Rosen, JA Purdy, "Computer Controlled Medical Accelerators," in *Advances in Radiation Oncology Physics: Dosimetry, Treatment Planning, and Brachytherapy*, edited by JA Purdy (American Institute of Physics 1992).
7. II Rosen, "Quality Assurance in Conformal Radiation Therapy," in *Radiation Therapy Physics*, edited by AR Smith (Springer-Verlag, 1995), pp. 449-455
8. II Rosen, "Treatment Planning for IMRT," in *The Theory and Practice of Intensity Modulated Radiation Therapy*, edited by ES Sternick (Advanced Medical Publishing, Madison, 1997), pp. 37-49.
9. KR Hogstrom, II Rosen, "Resources Needed to Support 3-D Radiation Therapy Treatment Planning," in *A Practical Guide to 3-D Planning and Conformal Radiation Therapy*, edited by JA Purdy and G Starkschall (Advanced Medical Publishing, Madison, 1999), pp. 341-358.
10. R Popple, II Rosen, "Delivery of Multiple IMRT Fields Using a Single Physical Attenuator," *The Use of Computers in Radiation Therapy*, edited by W Schlegel and T Bortfeld, Springer, Berlin, 191-193 (2000).
11. II Rosen, "Computer Optimization and Objective Functions," in *3-D Conformal and Intensity Modulated Radiation Therapy: Physics and Clinical Applications*, edited by JA Purdy, WH Grant III, JR Palta, EB Butler and CA Perez (Advanced Medical Publishing, Madison, 2001), pp. 231-245.
12. KR Hogstrom, JA Antolak, WF Hanson, JL Horton, II Rosen, AS Shiu, G Starkschall, "Clinical Radiation Physics," in *Radiation Oncology - Rationale, Technique, Results*, edited by JD Cox and KK Ang (Mosby, St. Louis, 2002), pp. 63-96.

Other Publications

1. I Rosen, F Einerson, "Shared editing with WPS-PLUS," *DEC Professional* 7, 78-80 (1988).
2. A Pollack, GK Zagars, JA Antolak, DA Kuban, II Rosen, "In response to Drs. Kagan and Schulz," *Int J Rad Onc Biol Phys* 55(4):1151-1152 (2003).
3. A Pollack, G Zagars, J Antolak, D Kuban, I Rosen, "In response to Drs. Millar and Williams," *Int J Rad Onc Biol Phys* 55(5):1461-1462 (2003).

Invited Presentations (Selected)

2006 "Treatment plan optimization in radiation therapy," Moffitt Cancer Center, Tampa, FL.

2005 "Treatment plan optimization in radiation therapy," UT Southwest Health Science Center, Dallas, TX.

2004 "Overview of clinical implementation of IMRT," 46th annual meeting of the American Association of Physicists in Medicine, Pittsburgh, PA.

2003 "CT and PET in radiation oncology treatment planning," UT M.D. Anderson Cancer Center Grand Rounds, Houston, TX.

2002 "Optimization and objective functions in radiation therapy," Refresher Course, RSNA annual meeting, Chicago, IL.

2002 "Guiding radiation therapy with daily CT imaging?" spring meeting, Southwest Chapter of the American Association of Physicists in Medicine, Dallas, TX.

2002 "Introduction to IMRT treatment planning," RadOnc2002 conference, UT M.D. Anderson Cancer Center, Houston, TX.

2001 "Imaging in Radiation Therapy", 19th annual meeting of the Houston Society for Engineering in Medicine and Biology, Houston, TX.

2000 "3D Conformal Radiation Therapy and IMRT", 25th annual congress of the Oncology Nursing Society, San Antonio, TX.

"Optimization and Cost Functions", 5th International Symposium on 3D Conformal Radiation Therapy and Brachytherapy, New York, NY.

1999 "Computer Optimization and Objective Functions," 4th International Symposium on 3-D Conformal Radiation Therapy and Intensity Modulated Radiation Therapy in the New Millennium, Houston, TX.

1998 "Treatment Plan Optimization." 70th annual meeting of the American Society of Radiologic Technologists, Houston, TX.

"Treatment Plan Optimization." 22nd annual ASRT Radiation Therapy Conference, Phoenix, AZ.

"Radiation Therapy Treatment Plan Optimization", Rice University, Houston, TX.

1997 "3D Treatment Planning and Conformal Radiation Therapy." Annual meeting of the Houston Medical Imaging Society, Houston, TX.

1996 "Treatment Planning for Intensity-Modulated Radiation Therapy." NOMOS Workshop on Intensity-Modulate Radiotherapy, Durango, CO.

"Treatment Plan Optimization." 21st annual meeting of the American Association of Medical Dosimetrists, Houston, TX.

"Writing Software for the Clinic." 38th annual meeting of the American Association of Physicists in Medicine, Philadelphia, PA.

1994 "Simulated Annealing Optimization for Radiation Oncology." Baylor College of Medicine, Houston, TX.

"Assessment of a Linear Accelerator for Segmented Conformal Radiation Therapy." National Cancer Institute Workshop on 3D Conformal Therapy, Bethesda, MD.

"Use of Simulated Annealing for Conformal Therapy Plan Optimization." 36th annual meeting of the American Association of Physicists in Medicine, Anaheim, CA.

1993 "Beam Optimization." Annual meeting and dosimetry workshop of the American Association of Medical Dosimetrists, League City, TX.

"Automated Treatment Planning for Computer-Controlled Radiotherapy." The University of Florida, Gainesville, FL.

1992 "Automated Treatment Planning for Conformal Radiation Therapy." 11th annual meeting of the European Society of Therapeutic Radiology and Oncology, Malmo, Sweden.

1991 "Radiotherapy Treatment Planning." The Houston Society for Engineering in Medicine and Biology, University of Houston, Houston, TX.

1990 "Computer Controlled Medical Accelerators." American Association of Physicists in Medicine, 1990 Summer School, Lawrence, KA.

"Treatment Plan Optimization Using Linear Programming Techniques." 9th annual meeting of the European Society of Therapeutic Radiology and Oncology, Montecatini Terme, Italy.

"Optimization of Treatment Plans Using Linear Programming and Simulated Annealing." UT M. D. Anderson Cancer Center, Houston, TX.

EXHIBIT 2

Isaac I. Rosen, Ph.D.
DABR, DABMP, FAAPM
Radiation Physicist

Professional Experience in Radiation Therapy Treatment Plan Optimization

Funded Research

1988-1995 Principal Investigator, "Conformal Radiation Therapy Treatment Plan Optimization." National Cancer Institute R01-CA46634, \$1,004,000 (total costs).
1991-1994 Co-investigator, "Mathematical Programming of Radiotherapy Plans." The Whitaker Foundation, \$180,000 (direct costs).
1992-1993 Principal Investigator, "Experimental Evaluation of Segmented Conformal Radiation Therapy." Houston Institute for Cancer Research, Detection and Treatment, \$35,000 (direct costs).

Session Chair at National and International Conferences

2003 American Association of Physicists in Medicine, 45th annual meeting, "IMRT: Planning and Optimization", San Diego, CA
2001 American Society for Therapeutic Radiology and Oncology, 43th annual meeting, "Treatment Planning and Evaluation", San Francisco, CA
2000 World Congress on Medical Physics and Biomedical Engineering, "Optimization 1", Chicago, IL
1999 International Symposium 3-D Conformal Radiation Therapy and Intensity Modulated Radiation Therapy in the New Millennium, "Treatment Plan Optimization", Houston, TX
1996 American Association of Physicist in Medicine, 38th annual meeting, "Treatment Planning", Philadelphia, PA
1994 American Association of Physicist in Medicine, 36th annual meeting, "Therapy: Treatment Planning and Delivery", Anaheim, CA
1993 American Society for Therapeutic Radiology and Oncology, 35th annual meeting, "Dynamic Therapy", New Orleans, LA

Refereed Publications

SM Morrill, II Rosen, RG Lane, JA Belli, "The Influence of dose constraint point placement on optimized radiation therapy treatment planning," Int. J. Rad. Onc. Biol. Phys. 19, 129-141 (1990).

RG Lane, MD Loyd, CH Chow, E Ekwelundu, II Rosen, "Improved dose homogeneity in the head and neck using computer controlled radiation therapy," Int. J. Rad. Onc. Biol. Phys. 19, 1531-1538 (1990).

SM Morrill, RG Lane, II Rosen, "Constrained simulated annealing for optimized radiation therapy treatment planning," Comp. Prog. Biomed. 33, 135-144 (1990).

II Rosen, RG Lane, SM Morrill, JA Belli, "Treatment plan optimization using linear programming," Med. Phys. 18, 141-152 (1991).

SM Morrill, RG Lane, G Jacobson, II Rosen, "Treatment planning optimization using constrained simulated annealing," Phys. Med. Biol. 36, 1341-1361 (1991).

SM Morrill, RG Lane, JA Wong, II Rosen, "Dose-volume considerations with linear programming optimization," Med. Phys. 18, 1201-1210 (1991).

RG Lane, MD Loyd, CH Chow, E Ekwelundu, II Rosen, "Custom beam profiles in computer-controlled radiation therapy," Int. J. Rad. Onc. Biol. Phys. 22, 167-174 (1992).

II Rosen, SM Morrill, RG Lane, "Optimized dynamic rotation with wedges," Med. Phys. 19, 971-977 (1992).

SM Morrill, ML Langer, RG Lane, II Rosen, "Tissue heterogeneity effects in treatment plan optimization," *Int. J. Rad. Onc. Biol. Phys.* 30, 699-706 (1994).

SM Morrill, KS Lam, RG Lane, M Langer, II Rosen, "Very fast simulated reannealing in radiation therapy treatment plan optimization," *Int. J. Rad. Onc. Biol. Phys.* 31, 179-188 (1995).

II Rosen, KS Lam, RG Lane, M Langer, SM Morrill, "Comparison of simulated annealing algorithms for conformal therapy treatment planning," *Int. J. Rad. Oncol. Biol. Phys.* 33(5), 1091-1099 (1995).

TR Willoughby, G Starkschall, NA Janjan, II Rosen, "Evaluation and scoring of radiotherapy treatment plans using an artificial neural network," *Int. J. Rad. Onc. Biol. Phys.* 34, 921-930 (1996).

AM Steadham, HH Liu, CH Crane, NA Janjan, II Rosen, "Optimization of beam orientations and weights for coplanar conformal beams in treating pancreatic cancer," *Med. Dosimetry* 24(4), 265-271 (1999).

HH Liu, II Rosen, NA Janjan, A Pollack, "Treatment planning optimization based on response-surface modeling of cost function versus multiple constraints," CD-ROM Proceedings of the 2000 World Congress on Medical Physics and Biomedical Engineering, 4 pp, July 23-28, Chicago (2000).

G Starkschall, RE Steadham, NH Wells, L O'Neill, LA Miller, II Rosen, "Monitor unit calculations as part of beam commissioning for a radiation treatment planning system," CD-ROM Proceedings of the 2000 World Congress on Medical Physics and Biomedical Engineering, 4 pp, July 23-28, Chicago (2000).

JC O'Daniel, L Dong, DA Kuban, H Liu, N Schechter, S Tucker, I Rosen, "The delivery of IMRT with a single physical modulator for multiple fields: a feasibility study for paranasal sinus cancer," *Int J Rad Onc Biol Phys* 58(3):876-887 (2004).

I Rosen, HH Liu, N Childress, Z Liao, "Interactively exploring optimized treatment plans," *Int J Rad Onc Biol Phys* 61:570-582 (2005).

Book Chapters

II Rosen, RG Lane, "Treatment Plan Optimization for Conformal Therapy," Proceedings of the Ninth International Conference on the Use of Computers in Radiation Therapy, Elsevier Science Publishers BV, The Netherlands, 357-360 (1987).

T Blake, PA Hickling, RG Lane, AE Nahum, II Rosen, ME Rosenbloom, "Assessment of the Philips SL25 Linac for Conformation Therapy," Proceedings of the Ninth International Conference on the Use of Computers in Radiation Therapy, Elsevier Science Publishers BV, The Netherlands, 537-540 (1987).

II Rosen, "Treatment Planning for IMRT," in *The Theory and Practice of Intensity Modulated Radiation Therapy*, edited by ES Sternick (Advanced Medical Publishing, Madison, 1997), pp. 37-49.

R Popple, II Rosen, "Delivery of Multiple IMRT Fields Using a Single Physical Attenuator," *The Use of Computers in Radiation Therapy*, edited by W Schlegel and T Bortfeld, Springer, Berlin, 191-193 (2000).

II Rosen, "Computer Optimization and Objective Functions," in *3-D Conformal and Intensity Modulated Radiation Therapy: Physics and Clinical Applications*, edited by JA Purdy, WH Grant III, JR Palta, EB Butler and CA Perez (Advanced Medical Publishing, Madison, 2001), pp. 231-245.

Invited Presentations (Selected)

- 2006 "Treatment plan optimization in radiation therapy," Moffitt Cancer Center, Tampa, FL.
- 2005 "Treatment plan optimization in radiation therapy," UT Southwest Health Science Center, Dallas, TX.
- 2002 "Optimization and objective functions in radiation therapy," Refresher Course, RSNA annual meeting, Chicago, IL.
- 2002 "Introduction to IMRT treatment planning," RadOnc2002 conference, UT M.D. Anderson Cancer Center, Houston, TX.

2000 "3D Conformal Radiation Therapy and IMRT", 25th annual congress of the Oncology Nursing Society, San Antonio, TX.
"Optimization and Cost Functions", 5th International Symposium on 3D Conformal Radiation Therapy and Brachytherapy, New York, NY.

1999 "Computer Optimization and Objective Functions," 4th International Symposium on 3-D Conformal Radiation Therapy and Intensity Modulated Radiation Therapy in the New Millenium, Houston, TX.

1998 "Treatment Plan Optimization." 70th annual meeting of the American Society of Radiologic Technologists, Houston, TX.
"Treatment Plan Optimization." 22nd annual ASRT Radiation Therapy Conference, Phoenix, AZ.
"Radiation Therapy Treatment Plan Optimization", Rice University, Houston, TX.

1997 "3D Treatment Planning and Conformal Radiation Therapy." Annual meeting of the Houston Medical Imaging Society, Houston, TX.

1996 "Treatment Planning for Intensity-Modulated Radiation Therapy." NOMOS Workshop on Intensity-Modulate Radiotherapy, Durango, CO.
"Treatment Plan Optimization." 21st annual meeting of the American Association of Medical Dosimetrists, Houston, TX.

1994 "Simulated Annealing Optimization for Radiation Oncology." Baylor College of Medicine, Houston, TX.
"Use of Simulated Annealing for Conformal Therapy Plan Optimization." 36th annual meeting of the American Association of Physicists in Medicine, Anaheim, CA.

1993 "Beam Optimization." Annual meeting and dosimetry workshop of the American Association of Medical Dosimetrists, League City, TX.
"Automated Treatment Planning for Computer-Controlled Radiotherapy." The University of Florida, Gainesville, FL.

1992 "Automated Treatment Planning for Conformal Radiation Therapy." 11th annual meeting of the European Society of Therapeutic Radiology and Oncology, Malmo, Sweden.

1990 "Computer Controlled Medical Accelerators." American Association of Physicists in Medicine, 1990 Summer School, Lawrence, KA.
"Treatment Plan Optimization Using Linear Programming Techniques." 9th annual meeting of the European Society of Therapeutic Radiology and Oncology, Montecatini Terme, Italy.
"Optimization of Treatment Plans Using Linear Programming and Simulated Annealing." UT M. D. Anderson Cancer Center, Houston, TX.

EXHIBIT 3

References

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Carol MP(1997B). Where we go from here: One person's vision. The theory and practice of intensity modulated radiation therapy. Ed: ES Sternick. Advanced Medical Publishing. pp 243-252.

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Kallman P, Lind BK, et al. (1992). "An algorithm for maximizing the probability of complication-free tumour control in radiation therapy." Phys Med Biol **37**: 871-890.

Kirkpatrick S, Gelatt CD, et al. (1983). "Optimization by simulated annealing." Science **220**: 671-680.

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Webb S (1992). "Optimization by simulated annealing of three-dimensional, conformal treatment planning for radiation fields defined by a multileaf collimator: II. Inclusion of two-dimensional modulation of the x-ray intensity." Phys Med Biol **37**: 1689-1704.

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Yu Y (1997). "Multiobjective decision theory for computational optimization in radiation therapy." Medical Physics **24**(9): 1445-1454.